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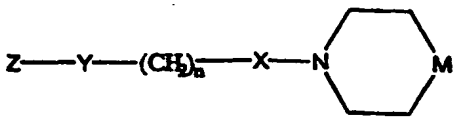

(I)

(57) Abstract

Disclosed are novel compounds and a method of treating a disease associated with aberrant leukocyte recruitment and/or activation. The method comprises administering to a subject in need an effective amount of a compound represented by structural formula (I) and physiologically acceptable salts thereof.

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CHEMOKINE RECEPTOR ANTAGONISTS AND METHODS OF USE THEREFOR

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Serial No. 09/148,515, filed September 4, 1998, which is a continuation -in-part of U.S. Serial No. 09/009,977, filed January 21, 1998, now abandoned, the entire teachings of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Chemoattractant cytokines or chemokines are a family of proinflammatory mediators that promote recruitment and activation of multiple lineages of leukocytes and lymphocytes. They can be released by many kinds of tissue cells after activation. Continuous release of chemokines at sites of inflammation mediates the ongoing migration of

effector cells in chronic inflammation. The chemokines characterized to date are related in primary structure. They share four conserved cysteines, which form disulfide bonds. Based upon this conserved cysteine motif, the family is divided into two main branches, designated as the C-X-C chemokines (α-chemokines), and the C-C chemokines (β-chemokines), in which the first two conserved cysteines are separated by an intervening residue, or adjacent respectively (Baggiolini, M. and Dahinden, C. A., *Immunology Today*, *15*:127-133 (1994)).

The C-X-C chemokines include a number of potent chemoattractants and activators of neutrophils, such as: interleukin 8 (IL-8), PF4 and neutrophil-activating peptide-2 (NAP-2). The C-C chemokines include RANTES (Regulated on Activation, Normal T Expressed and Secreted), the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β), eotaxin, and human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2, MCP-3), which have been characterized as chemoattractants and activators of monocytes or lymphocytes but do not appear to be chemoattractants for neutrophils. Chemokines, such as RANTES and MIP-1α, have been implicated in a wide range of human acute and chronic inflammatory diseases including respiratory diseases, such as asthma and allergic disorders.

The chemokine receptors are members of a superfamily of G protein-coupled receptors (GPCR) which share structural features that reflect a common mechanism of action of signal transduction (Gerard, C. and Gerard, N.P., *Annu Rev. Immunol.*, *12*:775-808 (1994); Gerard, C. and

Gerard, N. P., *Curr. Opin. Immunol.*, *6*:140-145 (1994)). Conserved features include seven hydrophobic domains spanning the plasma membrane, which are connected by hydrophilic extracellular and intracellular loops. The majority of the primary sequence homology occurs in the hydrophobic transmembrane regions with the hydrophilic regions being more diverse. The first receptor for the C-C chemokines that was cloned and expressed binds the chemokines MIP-1α and RANTES. Accordingly, this MIP-1α/RANTES receptor was designated C-C chemokine receptor 1 (also referred to as CCR-1; Neote, K., *et al.*, *Cell*, *72*:415-425 (1993); Horuk, R. *et al.*, WO 94/11504, May 26, 1994; Gao, J.-I. *et al.*, *J. Exp. Med.*, *177*:1421-1427 (1993)). Three receptors have been characterized which bind and/or signal in response to RANTES: CCR3 mediates binding and signaling of chemokines including eotaxin, RANTES, and MCP-3 (Ponath et al., *J. Exp. Med.*, *183*:2437 (1996)), CCR4 binds chemokines including RANTES, MIP-1α, and MCP-1 (Power, et al., *J. Biol. Chem.*, *270*:19495 (1995)), and CCR5 binds chemokines including MIP-1α, RANTES, and MIP-1β (Samson, *et al.*, *Biochem. 35*: 3362-3367 (1996)). RANTES is a chemotactic chemokine for a variety of cell types, including monocytes, eosinophils, and a subset of T-cells. The responses of these different cells may not all be mediated by the same receptor, and it is possible that the receptors CCR1, CCR4 and CCR5 will show some selectivity in receptor distribution and function between leukocyte types, as has already been shown for CCR3 (Ponath *et al.*). In particular, the ability of RANTES to induce the directed migration of monocytes and a memory

population of circulating T-cells (Schall, T. et al., *Nature*, 347:669-71 (1990)) suggests this chemokine and its receptor(s) may play a critical role in chronic inflammatory diseases, since these diseases are characterized by destructive infiltrates of T cells and monocytes.

Many existing drugs have been developed as antagonists of the receptors for biogenic amines, for example, as antagonists of the dopamine and histamine receptors. No successful antagonists have yet been developed to the receptors for the larger proteins such as chemokines and C5a. Small molecule antagonists of the interaction between C-C chemokine receptors and their ligands, including RANTES and MIP-1α, would provide compounds useful for inhibiting harmful inflammatory processes "triggered" by receptor ligand interaction, as well as valuable tools for the investigation of receptor-ligand interactions.

SUMMARY OF THE INVENTION

It has now been found that a class of small organic molecules are antagonists of chemokine receptor function and can inhibit leukocyte activation and/or recruitment. An antagonist of chemokine receptor function is a molecule which can inhibit the binding and/or activation of one or more chemokines, including C-C chemokines such as RANTES, MIP-1α, MCP-2, MCP-3 and/or MCP-4 to one or more chemokine receptors on leukocytes and/or other cell types. As a consequence, processes and cellular responses mediated by chemokine receptors can be inhibited with these small organic molecules. Based on this discovery, a method of

treating a subject with a disease associated with aberrant leukocyte recruitment and/or activation is disclosed as well as a method of treating a disease mediated by chemokine receptor function. The method comprises administering to a subject in need of treatment an effective amount of a compound or small organic molecule which is an antagonist of chemokine receptor function. Compounds or small organic molecules which have been identified as antagonists of chemokine receptor function are discussed in detail herein below, and can be used for the manufacture of a medicament for treating or for preventing a disease associated with aberrant leukocyte recruitment and/or activation. The invention also relates to the disclosed compounds and small organic molecules for use in treating or preventing a disease associated with aberrant leukocyte recruitment and/or activation. The invention also includes pharmaceutical compositions comprising one or more of the compounds or small organic molecules which have been identified herein as antagonists of chemokine function and a suitable pharmaceutical carrier. The invention further relates to novel compounds which can be used to treat an individual with a disease associated with aberrant leukocyte recruitment and/or activation and methods for their preparation.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic showing the preparation of the compounds represented by Structural Formulas (I) and (II).

Figure 2 is a schematic showing the preparation of representative compounds Structural Formula (I) and (II),

wherein Z is represented by Structural Formulas (IV) and wherein Ring A and/or Ring B in Z can be substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$.

Figure 3 is a schematic showing the preparation of the compounds represented by Structural Formula (I) and (II), wherein Z is represented by Structural Formulas (VIII) and (XIII)-(XVIc) and wherein V is W_a.

Figure 4 is a schematic showing the preparation of compounds represented by Structural Formulas (I) and (II), wherein Z is represented by Structural Formula (IV), wherein W is H.

Figure 5 is a schematic showing the preparation of compounds represented by Structural Formulas (I) and (II), wherein Z is represented by Structural Formula (IV), wherein W is H.

Figure 6A-6AD shows the structures of a number of exemplary compounds of the present invention.

Figure 7 shows the preparation of compounds represented by Structural Formula (I), where in Z is represented by Structural Formulas (VI) and wherein Ring A and/or Ring B in Z is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, u is one.

Figure 8 shows the preparation of compounds represented by Structural Formula (I), wherein Z is represented by Structural Formulas (VI) and wherein Ring A or Ring B in Z is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, u is zero.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to small molecule compounds which are modulators of chemokine receptor function. In a preferred embodiment, the small molecule compounds are antagonists of chemokine receptor function. Accordingly, processes or cellular responses mediated by the binding of a chemokine to a receptor can be inhibited (reduced or prevented, in whole or in part), including leukocyte migration, integrin activation, transient increases in the concentration of intracellular free calcium $[Ca^{++}]_i$, and/or granule release of proinflammatory mediators.

The invention further relates to a method of treatment, including prophylactic and therapeutic treatments, of a disease associated with aberrant leukocyte recruitment and/or activation or mediated by chemokines or chemokine receptor function, including chronic inflammatory disorders characterized by the presence of RANTES, MIP-1α, MCP-2, MCP-3 and/or MCP-4 responsive T cells, monocytes and/or eosinophils, including but not limited to diseases such as arthritis (e.g., rheumatoid arthritis), atherosclerosis, arteriosclerosis, ischemia/reperfusion injury, diabetes mellitus (e.g., type 1 diabetes mellitus), psoriasis, multiple sclerosis, inflammatory bowel diseases such as ulcerative colitis and Crohn's disease, rejection of transplanted organs and tissues (i.e., acute allograft rejection, chronic allograft rejection), graft versus host disease, as well as allergies and asthma. Other diseases associated with aberrant leukocyte recruitment and/or activation which can be treated (including prophylactic

treatments) with the methods disclosed herein are inflammatory diseases associated with Human Immunodeficiency Virus (HIV) infection, e.g., AIDS associated encephalitis, AIDS related maculopapular skin eruption, AIDS related interstitial pneumonia, AIDS related enteropathy, AIDS related periportal hepatic inflammation and AIDS related glomerulo nephritis. The method comprises administering to the subject in need of treatment an effective amount of a compound (i.e., one or more compounds) which inhibits chemokine receptor function, inhibits the binding of a chemokine to leukocytes and/or other cell types, and/or which inhibits leukocyte migration to, and/or activation at, sites of inflammation.

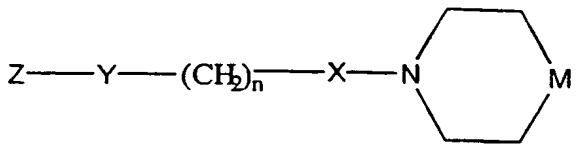
The invention further relates to methods of antagonizing a chemokine receptor, such as CCR1, in a mammal comprising administering to the mammal a compound as described herein.

According to the method, chemokine-mediated chemotaxis and/or activation of pro-inflammatory cells bearing receptors for chemokines can be inhibited. As used herein, "pro-inflammatory cells" includes but is not limited to leukocytes, since chemokine receptors can be expressed on other cell types, such as neurons and epithelial cells.

While not wishing to be bound by any particular theory or mechanism, it is believed that compounds of the invention are antagonists of the chemokine receptor CCR1, and that therapeutic benefits derived from the method of the invention are the result of antagonism of CCR1 function. Thus, the method and compounds of the invention can be used to treat a medical condition involving cells

which express CCR1 on their surface and which respond to signals transduced through CCR1, as well as the specific conditions recited above.

In one embodiment of the present invention, the antagonist of chemokine receptor function is represented by Structural Formula (I):



(I)

Z is a cycloalkyl or non-aromatic heterocyclic ring fused to one or more carbocyclic aromatic rings and/or heteroaromatic rings.

Y is a covalent bond, -O-, -CO- or =CH-.

n is an integer, such as an integer from one to about five. n is preferably one, two, or three. In alternative embodiments, other aliphatic or aromatic spacer groups (L) can be employed for $(CH_2)_n$.

X is a covalent bond or -CO-.

M is $>NR^2$ or $>CR^1R^2$. Preferably, M is $>C(OH)R^2$.

R^1 is -H, -OH, $-N_3$, halogen, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group),

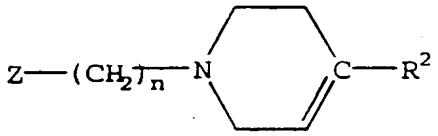
-SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -C(O)O-(aliphatic group), -C(O)O-(substituted aliphatic group), -COOH, -CN, $-CO-NR^3R^4$, $-NR^3R^4$; or R^1 can be a covalent bond between the ring atom at M and an adjacent carbon atom in the ring which contains M. R^1 is preferably -H or -OH.

R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group. R^2 is preferably an aromatic group or a substituted aromatic group.

R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group.

R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, can alternatively form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring.

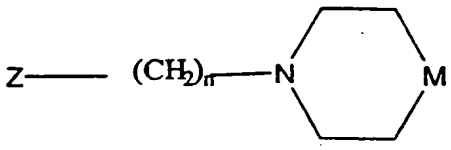
In embodiments where M is $>CR^1R^2$ and R^1 is a covalent bond between the carbon atom at M and an adjacent carbon atom in the ring which contains M, the antagonist of chemokine function can be represented by Structural Formula (Ia).



(Ia)

Z, n, and R^2 are as described in Structural Formula (I).

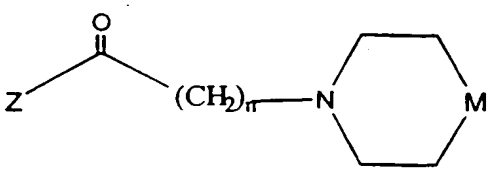
In a preferred embodiment, -X- and -Y- in Structural Formula (I) are each a covalent bond and the antagonist of chemokine receptor function is a compound represented by Structural Formula (II):



(II)

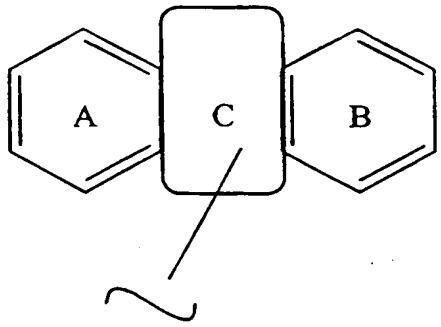
Z, n and M are as described above for Structural Formula (I).

In another preferred embodiment, -X- is a covalent bond, -Y- is -CO- and the antagonist of chemokine receptor function is a compound represented by Structural Formula (III):



(III)

Preferably, Z is a tricyclic ring system comprising two carbocyclic aromatic groups fused to a six, seven or eight membered cycloalkyl group or to a non-aromatic heterocyclic ring. In one example, Z is represented by Structural Formula (IV):



(IV)

The phenyl rings in Structural Formula (IV), labeled with an "A" and "B", are referred to herein as "Ring A" and "Ring B", respectively. The central ring, labeled with a "C", is referred to as "Ring C" and can be, for example, a six, seven or eight membered non-aromatic carbocyclic ring (e.g., a cycloheptane or cyclooctane ring) or a non-aromatic heterocyclic ring. When Ring C is a non-aromatic heterocyclic ring, it can contain one or two heteroatoms such as nitrogen, sulfur or oxygen. When Z is represented by Structural Formula (IV), the tricyclic ring system can be connected to Y in Structural Formula (I) by a single covalent bond between Y and a ring atom in Ring C.

Ring A and/or Ring B can be unsubstituted. Alternatively, Ring A and/or Ring B can have one or more substituents. Suitable substituents are as described herein below. In one example, Ring A or Ring B is substituted with $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}-$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$.

u is zero or one.

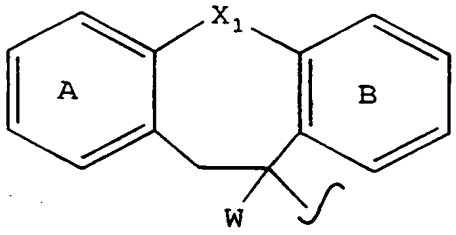
t is an integer, such as an integer from zero to about three, and the methylene group, $-(CH_2)_t-$, can be substituted or unsubstituted.

R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group. Alternatively, R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, can form a non-aromatic heterocyclic ring.

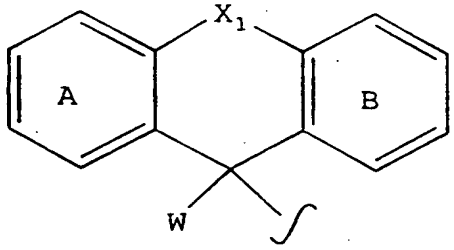
Ring C optionally contains one or more substituents as described herein below. Preferably, Ring C is unsubstituted or substituted with an electron withdrawing group. Suitable electron withdrawing groups include -CN, $-CH_2=NH$, alkylimines, alkylsulfonyl, carboxamido, carboxylic alkyl esters, $-NO_2$ and halogens (e.g., -Br and -Cl). Alternatively, Ring C is substituted with a group selected from $-CH_2-NR^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$.

R^{11} and R^{12} are independently -H, an aliphatic group a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group. Alternatively, R^{11} and R^{12}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

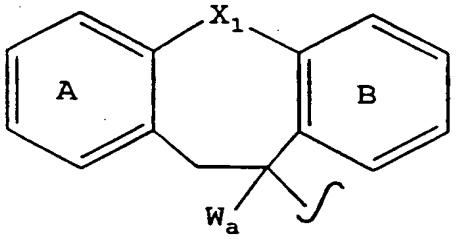
Examples of suitable tricyclic rings systems represented by Structural Formula (IV) are provided by Structural Formula (V)-(VIII), shown below:



(V)



(VI)



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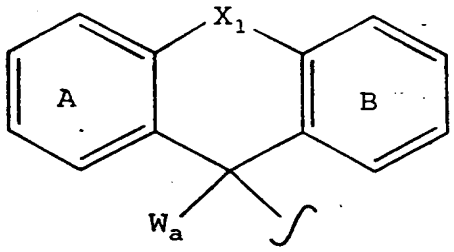


(VIII)

X_1 is a covalent bond, -S-, $-CH_2-$ or $-CH_2-S-$. Preferably, X_1 is -S- in Structural Formulas (V) and (VII). Preferably, X_1 is $-CH_2-S-$ in Structural Formulas (VI) and (VIII).

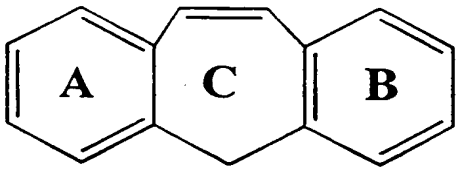
W is -H or an electron withdrawing group, as described above for Structural Formula (IV). A preferred electron withdrawing group is -CN.

W_a is a group selected from $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$.

R^{11} and R^{12} are as defined in Structural Formula (IV).

Ring A and Ring B in Structural Formulas (V)-(VIII) can be as described above in Structural Formula (IV).

Other examples of suitable tricyclic ring systems represented by Structural Formula (IV) are shown below in Structural Formulas (XI), (XII), (XIIa), (XIIb) and (XIIc):



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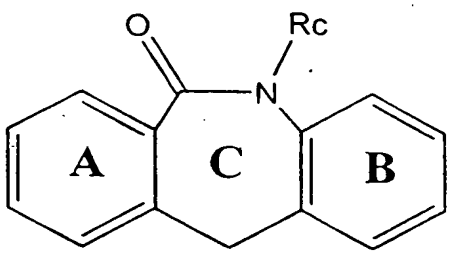

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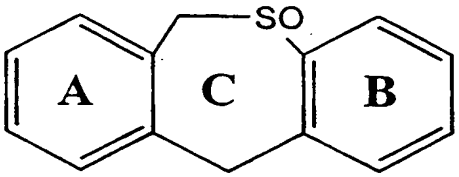
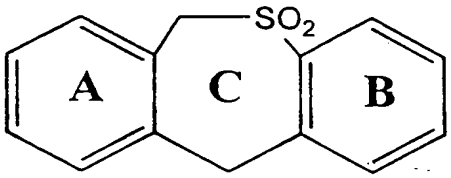
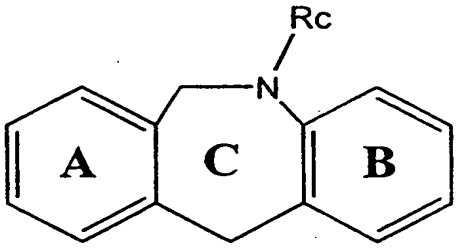


(XIIa)



(XIIb)



(XIIc)

Rings A-C in Structural Formulas (XI)-(XII), (XIIa), (XIIb) and (XIIc) can be as described for Structural Formula (IV).

R_c is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group.

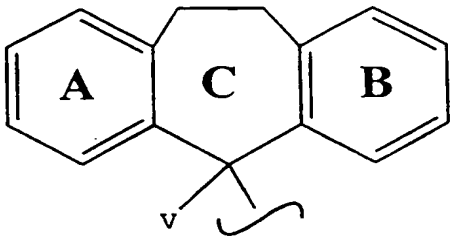
Preferably, R_c is a substituted C_1-C_{20} aliphatic group, a

C_1-C_{20} aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group. In one example, R_c is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-OC(O)R^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$.

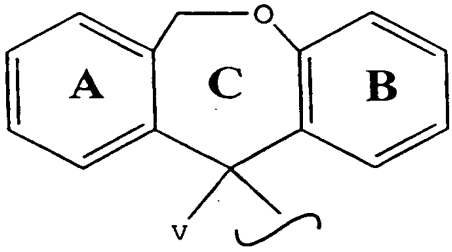
s is an integer from one to about three.

R^{30}, R^{31}, and R^{32} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a substituted or unsubstituted non-aromatic heterocyclic group. Alternatively, R^{31} and R^{32}, taken together with the nitrogen atom to which they are bonded, can form a non-aromatic heterocyclic ring.

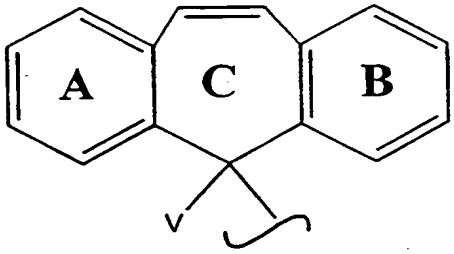
Preferred examples of tricyclic ring systems represented by Structural Formulas (XI)-(XII), (XIIa), (XIIb) and (XIIc) are shown below in Structural Formulas (XIII)-(XVI), (XVIa), (XVIb) and (XVIc):



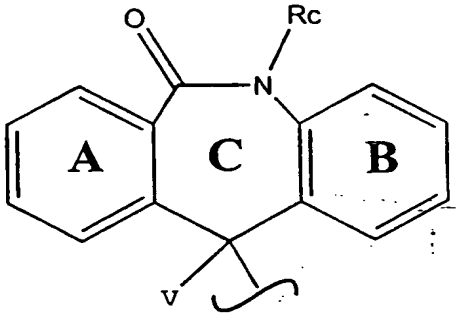
(XIII)



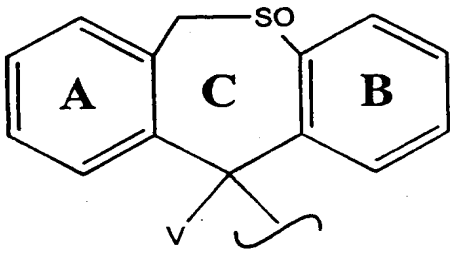
(XIV)



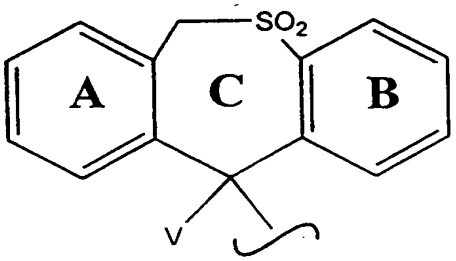
(XV)



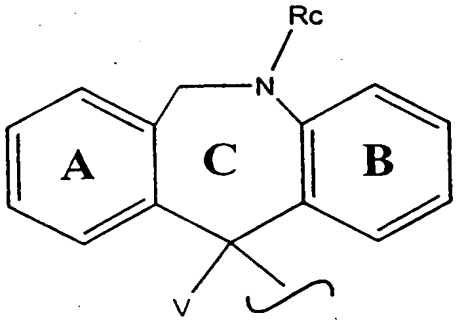
(XVI)



(XVIa)



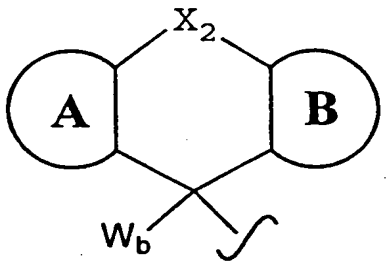
(XVIb)



(XVIc)

V can be W or W_a, which are as described above for Structural Formula (V)-(VIII).

In another preferred embodiment, Z is a tricyclic ring system comprising one or more aromatic groups (i.e., heteroaryl or aromatic carbocyclic) fused to a six, seven or eight membered cycloalkyl group or to a non-aromatic heterocyclic ring. Examples are represented by Structural Formula (XVII):



(XVII)

wherein X_2 is $-S-CH_2-$, $-CH_2-S-$, $-CH_2-O-$, $-O-CH_2-$, $-CO-NR_c-$, $-NR_c-CO-$, $-CH_2-S(O)_2-$, $-S(O)_2-CH_2-$, $-CH_2-NR_c-$, $-Nr_c-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2-SO-$, $-SO-CH_2-$;

Ring A and Ring B in Structural Formulas (XVII) are independently substituted or unsubstituted aromatic groups.

In one example, Ring A is a substituted or unsubstituted heteroaryl group and Ring B is a substituted or unsubstituted aromatic carbocyclic group. In another example Ring A and Ring B are independently substituted or

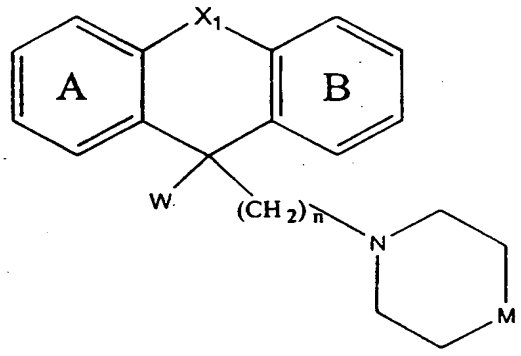
unsubstituted heteroaryl groups. In yet another example Ring A is a substituted or unsubstituted heteroaryl group, preferably a pyridyl group, and Ring B is a substituted or unsubstituted phenyl group. Ring A and/or Ring B can be substituted with R^{40}, which is a substituent as described herein. Preferably, R^{40} is an aliphatic group, substituted aliphatic group, -O-(aliphatic group) or -O-(substituted aliphatic group). More preferably, R^{40} is -O-alkyl, such as $-O-CH_3$, $-O-C_2H_5$, $-O-C_3H_7$ or $-O-C_4H_9$.

In a preferred embodiment, Ring A is a pyridyl group, Ring B is a phenyl group, and Ring B is substituted para to the carbon atom in Ring B that is also bonded to X_2 in Ring C.

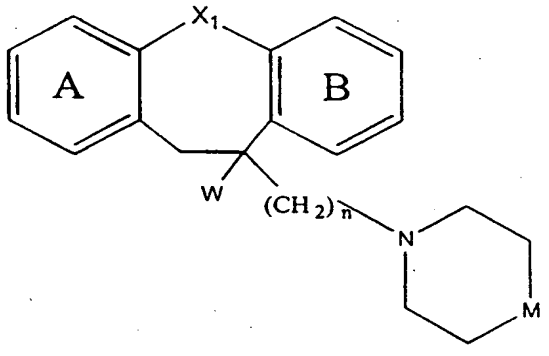
W_b is -H, -CH=NH, -CN, $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$.

R^{11} and R^{12} are as defined above for Structural Formula (IV).

In yet another preferred embodiment, the antagonist of chemokine function is a compound represented by Structural Formula (XXII) and (XXIII):



(XXII)

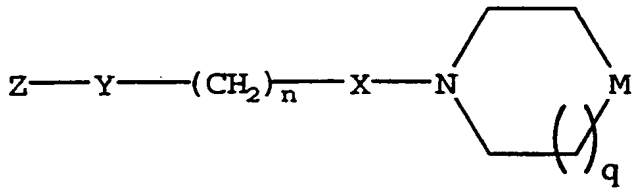


(XXIII)

In Structural Formulas (XXII) and (XXIII), X_1 can be as defined above for Structural Formulas (V) and (VI); n is an integer from two to five; W can be -H, -CN, -CH=NH, an electron withdrawing group, $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$.

In Structural Formulas (XXII) and (XXIII), Ring A can be substituted with R^8 and R^9, wherein R^8 and R^9 are independently -H, a halogen, alkoxy or alkyl, or, taken together with Ring A, form a naphthyl group. M is >N(alkanoyl), >N(aroyl), >N(aralkoyl), >N(alkyl), >N(aralkyl), >N(cycloalkyl), >C(OH)(aryl) or >CH(heteroaryl).

In another embodiment, the antagonist of chemokine activity can be represented by Structural Formula (XXIV):



(XXIV)

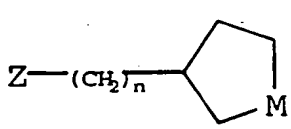
and physiologically acceptable salts thereof.

n, Y, X and M are as described in Structural Formula (I).

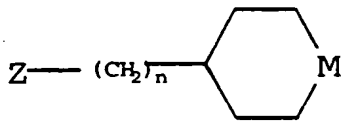
Z is as described in Structural Formulas (IV) - (VIII) and/or (XI)-(XVII).

q is an integer, such as an integer from zero to about three, and the ring containing M can be substituted or unsubstituted.

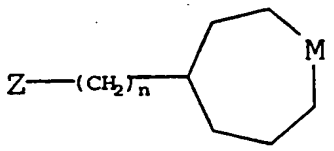
Thus, the antagonist of chemokine function can be represent by, for example, Structural Formulas (XXIVa)-(XXIVd):



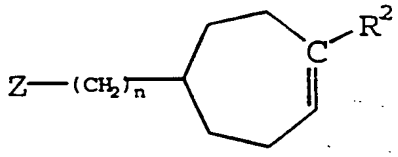
(XXIVa)



(XXIVb)



(XXIVc)



(XXIVd)

and physiologically acceptable salts thereof, wherein Z, n and M are as described in Structural Formula (XXIV), and the ring which contains M is substituted or unsubstituted.

Another embodiment of the invention provides novel compounds employed in these methods.

Also included in the present invention are physiologically acceptable salts of the compounds represented by Structural Formulas (I) through (XXIVd). Salts of compounds containing an amine or other basic group can be obtained, for example, by reacting with a suitable organic or inorganic acid, such as hydrogen chloride, hydrogen bromide, acetic acid, citric acid, perchloric acid and the like. Compounds with a quaternary ammonium group also contain a counteranion such as chloride, bromide,

iodide, acetate, perchlorate and the like. Salts of compounds containing a carboxylic acid or other acidic functional group can be prepared by reacting with a suitable base, for example, a hydroxide base. Salts of acidic functional groups contain a countercation such as sodium, potassium, ammonium, calcium and the like.

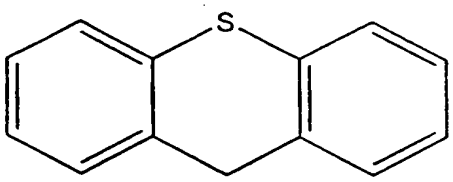
As used herein, aliphatic groups include straight chained, branched or cyclic C_1-C_8 hydrocarbons which are completely saturated or which contain one or more units of unsaturation. For example, suitable aliphatic groups include substituted or unsubstituted linear, branched or cyclic C_1-C_{20} alkyl, alkenyl or alkynyl groups.

An "alkyl group" is a saturated aliphatic group, as defined above. The term "alkoxy" refers to an alkyl ether chain with an alkyl group. "Alkanoyl" refers to alkyl substituted carbonyl; "aralkanoyl" refers to phenyl-alkyl-CO- and "aroyl" refers to arylcarbonyl including benzoyl, naphthoyl and the like. The term "halogen" means fluoro, chloro, bromo and iodo. The term "substituted phenyl" means phenyl substituted by alkyl, halogen, alkoxy, nitro, amino, acetamido, cyano and trifluoromethyl and naphthyl. "Aralkyl" means $-(CH_2)_x$-aryl, wherein x is an integer from one to four including benzyl.

Aromatic groups include carbocyclic aromatic groups such as phenyl, 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl, and heterocyclic aromatic or heteroaryl groups such as *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 3-pyridazinyl,

4-pyridazinyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyrazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 5-tetrazolyl, 2-oxazolyl, 4-oxazolyl and 5-oxazolyl. Where these rings are fused, for example, to Ring C, the stated point of attachment can be either of the two fused bonds.

Aromatic groups also include fused polycyclic aromatic ring systems in which a carbocyclic aromatic ring or heteroaryl ring is fused to one or more other rings. Examples include tetrahydronapthyl, 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 3-indolyl, 2-quinolinyl, 3-quinolinyl, 2-benzothiazolyl, 2-benzooxazolyl, 2-benzimidazolyl, 2-quinolinyl, 3-quinolinyl, 1-isoquinolinyl, 3-isoquinolinyl, 1-isoindolyl, 3-isoindolyl, and acridinyl. Also included within the scope of the term "aromatic group", as it is used herein, is a group in which one or more carbocyclic aromatic rings and/or heteroaryl rings are fused to a cycloalkyl or non-aromatic heterocyclic ring. Examples include benzocyclopentane, benzocyclohexane, decalin, phthalimido, benzodiazepines, benzooxazepines, benzooxazines, phenothiazines, and groups represented by the following structural formulas:



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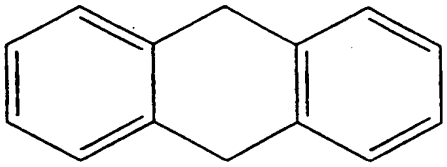

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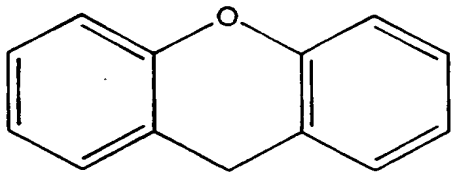

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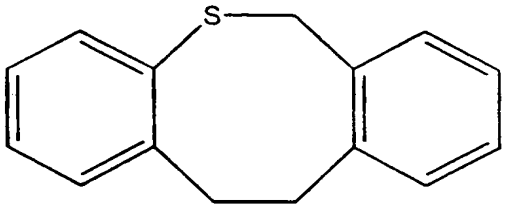

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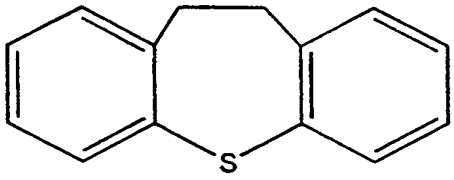

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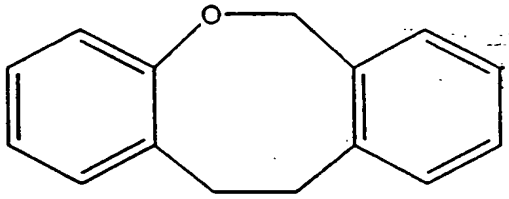

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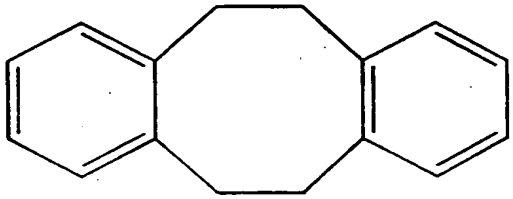
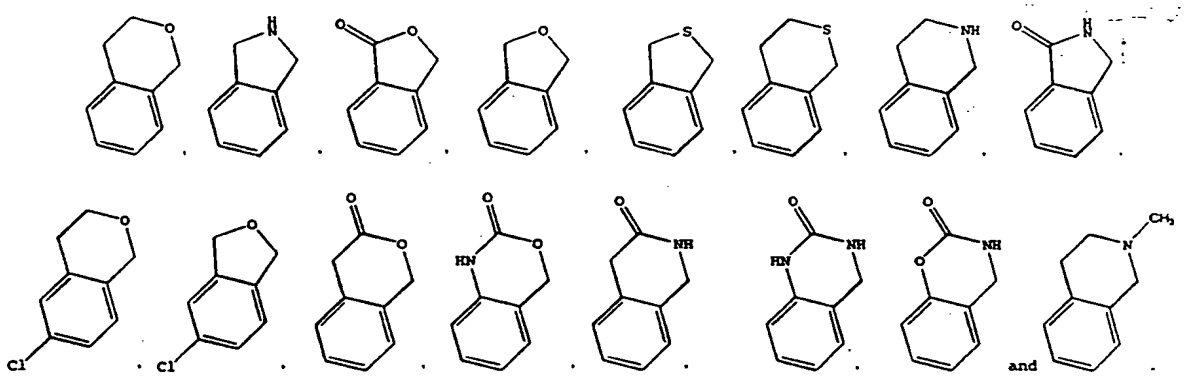
or



Non-aromatic heterocyclic rings are non-aromatic carbocyclic rings which include one or more heteroatoms such as nitrogen, oxygen or sulfur in the ring. The ring can be five, six, seven or eight-membered and/or fused to another ring, such as a cycloalkyl or aromatic ring. Examples include 3-1H-benzimidazol-2-one, 3-1-alkyl-benzimidazol-2-one,

3-1-methyl-benzimidazol-2-one, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahyrothiophenyl, 3-tetrahyrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl , 4-thiazolidinyl, diazolonyl, N-substituted diazolonyl, 1-phthalimidyl, 1-3-alkyl-phthalimidyl, benzoxane, benzopyrolidine, benzopiperidine, benzoxolane, benzothiolane, benzothiane,



"Heterocyclic ring", includes "heteroaryl group" and "non-aromatic heterocylic ring", and is defined as imidazole, benzimidazole, pyridine, pyrimidine, thiazole, benzothiazole, thienyl, benzothienyl.

Suitable substituents on an alkyl, aliphatic, aromatic, non-aromatic heterocyclic ring or benzyl group include, for example, an electron withdrawing group, an aliphatic group, substituted aliphatic group, azido, -OH, a

halogen (-Br, -Cl, -I and -F), -O-(aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group), -CN, $-NO_2$, -COOH, $-NH_2$, -NH(aliphatic group, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group), -N-(aliphatic group, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group)$_2$, -COO(aliphatic group, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group), $-CONH_2$, -CONH(aliphatic, substituted aliphatic group, benzyl, substituted benzyl, aromatic or substituted aromatic group), -CON(aliphatic, substituted aliphatic group, benzyl, substituted benzyl, aromatic or substituted aromatic group)$_2$, -SH, $-SO_k$(aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group) (k is 0, 1 or 2), $-NH-C(=NH)-NH_2$, $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$;

R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group, and wherein R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, can form a non-aromatic heterocyclic ring.

u is an integer such as zero or one.

t is an integer, such as an integer from zero to about three, and the methylene group, $-(CH_2)_t-$, can be substituted or unsubstituted.

A substituted non-aromatic heterocyclic ring, benzyl group or aromatic group can also have an aliphatic or

substituted aliphatic group, as a substituent. A substituted alkyl or aliphatic group can also have a non-aromatic heterocyclic ring, benzyl, substituted benzyl, aromatic or substituted aromatic group as a substituent. A substituted non-aromatic heterocyclic ring can also have =O, =S, =NH or =N(aliphatic, aromatic or substituted aromatic group) as a substituent. A substituted aliphatic, substituted aromatic, substituted non-aromatic heterocyclic ring or substituted benzyl group can have more than one substituent.

Suitable electron withdrawing groups include, for example, alkylimines, alkylsulfonyl, carboxamido, carboxylic alkyl esters, -CH=NH, -CN, $-NO_2$ and halogens.

Acyl groups include substituted and unsubstituted aliphatic carbonyl, aromatic carbonyl, aliphatic sulfonyl and aromatic sulfonyl.

The compounds disclosed herein can be obtained as different sterioisomers (e.g., diastereomers and enantiomers). For example, when the antagonist of chemokine receptor function is represented by Structural Formula (I) and Z is represented by Structural Formula (IV), the carbon atom in Ring C which is bonded to Y may be in the R or S sterioconfiguration. It is pointed out that the invention includes all isomeric forms and racemic mixtures of the disclosed compounds and a method of treating a subject with both pure isomers and mixtures thereof, including racemic mixtures. It is understood that one sterioisomer may be more active than another. The desired isomer can be determined by screening for activity, employing the methods described herein.

In the structural formulas depicted herein, the single or double bond by which a chemical group or moiety is connected to the remainder of the molecule or compound is indicated by the following symbol:

" ∫ "

For example, the corresponding symbol in Structural Formula (V) or (VIII) indicates that the tricyclic ring system, which represents Z in Structural Formula (I), is connected to the alkylene group in Structural Formula (I) by a single covalent bond between the alkylene group and the ring carbon in Ring C which is bonded to W.

A "subject" is preferably a bird or mammal, such as a human, but can also be an animal in need of veterinary treatment, e.g., domestic animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, fowl, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

An "effective amount" of a compound is an amount which results in the inhibition of one or more processes mediated by the binding of a chemokine to a receptor in a subject with a disease associated with aberrant leukocyte recruitment and/or activation. Examples of such processes include leukocyte migration, integrin activation, transient increases in the concentration of intracellular free calcium $[Ca^{2+}]_i$ and granule release of proinflammatory mediators. Alternatively, an "effective amount" of a compound is a quantity sufficient to achieve a desired therapeutic and/or prophylactic effect, such as an amount

which results in the prevention of or a decrease in the symptoms associated with a disease associated with aberrant leukocyte recruitment and/or activation.

The amount of compound administered to the individual will depend on the type and severity of the disease and on the characteristics of the individual, such as general health, age, sex, body weight and tolerance to drugs. It will also depend on the degree, severity and type of disease. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. Typically, an effective amount of the compound can range from about 0.1 mg per day to about 100 mg per day for an adult. Preferably, the dosage ranges from about 1 mg per day to about 100 mg per day. An antagonist of chemokine receptor function can also be administered in combination with one or more additional therapeutic agents, e.g. theophylline, β-adrenergic bronchodilators, corticosteroids, antihistamines, antiallergic agents, immunosuppressive agents (e.g., cyclosporin A, FK-506, prednisone, methylprednisolone) and the like.

The compound can be administered by any suitable route, including, for example, orally in capsules, suspensions or tablets or by parenteral administration. Parenteral administration can include, for example, systemic administration, such as by intramuscular, intravenous, subcutaneous, or intraperitoneal injection. The compound can also be administered orally (e.g., dietary), topically, transdermally, by inhalation (e.g., intrabronchial, intranasal, oral inhalation or intranasal drops), or rectally, depending on the disease or condition

to be treated. Oral or parenteral administration are preferred modes of administration.

The compound can be administered to the individual in conjunction with an acceptable pharmaceutical or physiological carrier as part of a pharmaceutical composition for treatment of HIV infection, inflammatory disease, or the other diseases discussed above. Formulation of a compound to be administered will vary according to the route of administration selected (e.g., solution, emulsion, capsule). Suitable carriers may contain inert ingredients which do not interact with the compound. Standard pharmaceutical formulation techniques can be employed, such as those described in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. Suitable pharmaceutical carriers for parenteral administration include, for example, sterile water, physiological saline, bacteriostatic saline (saline containing about 0.9% mg/ml benzyl alcohol), phosphate-buffered saline, Hank's solution, Ringer's-lactate and the like. Methods for encapsulating compositions (such as in a coating of hard gelatin or cyclodextran) are known in the art (Baker, *et al.*, "Controlled Release of Biological Active Agents", John Wiley and Sons, 1986).

The activity of compounds of the present invention can be assessed using suitable assays, such as receptor binding assays and chemotaxis assays. For example, as described in the Exemplification Section, small molecule antagonists of RANTES and MIP-1α binding have been identified utilizing THP-1 cells which bind RANTES and chemotax in response to RANTES and MIP-1α as a model for leukocyte chemotaxis.

Specifically, a high through-put receptor binding assay, which monitors ^{125}I-RANTES and ^{125}I-MIP-1α binding to THP-1 cell membranes, was used to identify small molecule antagonists which block binding of RANTES and MIP-1α. Compounds of the present invention can also be identified by virtue of their ability to inhibit the activation steps triggered by binding of a chemokine to its receptor, such as chemotaxis, integrin activation and granule mediator release. They can also be identified by virtue of their ability to block RANTES and MIP-1α mediated HL-60, T-cell, peripheral blood mononuclear cell, and eosinophil chemotactic response.

The compounds disclosed herein can be prepared accordingly to the schemes shown in Figures 1-5 and 7-8. The schemes are described in greater detail below.

Figure 1 is a schematic showing the preparation of the compounds represented by Structural Formulas (I) and (II), wherein Z is represented by Structural Formula (IV), wherein W is CN.

L^1, L^2 and L^3 in Figure 1 are suitable leaving groups such as halogen; p-toluene sulfonate, mesylate, alkoxy and phenoxy. The other symbols are as defined above.

The reduction reaction in Step 1 of Figure 1 is performed with a reducing agent such as or sodium borohydride or lithium aluminum hydride (LAH) in an inert solvent such as methanol or tetrahydrofuran (THF). The reaction is carried out at temperatures ranging from 0°C up to the reflux temperature and for 5 minutes to 72 h. Compounds represented by formula II in Figure 1 can be prepared by procedures disclosed in JP 61/152673, U.S.

Patent 5089496, WO 89/10369, WO 92/20681 and WO 93/02081, the entire teachings of which are incorporated herein by reference.

A chlorination reaction in step 2 of Figure 1 can be performed with reagents such as thionyl chloride. The reaction can be carried out in an inert solvent such as methylene chloride at 0°C up to the reflux temperature for 5 minutes to 72 h. The hydroxy group can be also converted to other leaving groups by methods familiar to those skilled in the art.

The cyanation reaction in step 3 of Figure 1 can be carried out using reagents such as copper cyanide, silver cyanide or sodium cyanide in an inert solvent such as benzene or toluene. Reaction temperatures range from 0°C up to the reflux temperature for 5 minutes to 72 h. Compounds represented by Formula V in Figure 1 can also be prepared by the procedures described in J. Med. Chem. 1994, 37, 804-810 and U.S. Patent 5672611, the entire teachings of which are incorporated herein by reference.

The alkylation reactions in steps 4 and 5 of Figure 1 can be carried out in a solvent such as acetone, methyl ethyl ketone, ethyl acetate, toluene, tetrahydrofuran (THF) or dimethylformamide (DMF) in the presence of a base such as potassium carbonate or sodium hydride and a catalyst such as an alkali metal iodide (when necessary). The reaction temperature can range from room temperature up to the reflux temperature and for 5 minutes to 72 h.

The product of the synthetic scheme shown in Figure 1 can be decyanated using a reducing agent such as lithium aluminum hydride (LAH) in an inert solvent such as ether or

tetrahydrofuran (THF) at 0°C up to the reflux temperature for the solvent used for 5 minutes to 72 h.

Figure 2 is a schematic showing the preparation of representative compounds of Structural Formula (I) and (II), wherein Z is represented by Structural Formulas (IV) and wherein Ring A and/or Ring B in Z can be substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$.

In Figure 2, the hydrolysis reaction may be carried out in a mixture of aqueous alkali metal hydroxide solution and a solvent such as methanol, ethanol, tetrahydrofuran (THF) or dioxane at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h. The acylation reaction can be carried out using dicyclohexylcarbodiimide (DCC) or (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (DEC) in a solvent such as tetrahydrofuran (THF), dimethylformamide (DMF) or methylene chloride in the presence of a base such as pyridine or triethylamine (when necessary) at temperatures of 0 to 100°C for 5 minutes to 72 h.

Compounds represented by Structural Formulas (I) and (II), wherein Z is represented by Structural Formulas (XVI), X is $-CO-N(R_c)-$ and R_c is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$, can be prepared by suitable modification of the scheme shown in Figure 1. One modification utilizes the starting material shown in Figure 1, wherein X is -CO-NH-. The amide is then alkylated with $L^3-(CH_2)_s-COOR^{30}$ using the alkylation procedures described above. L^3 is a suitable leaving

group. The remainder of the synthesis is as described in Figures 1 and 2.

Figure 3 is a schematic showing the preparation of the compounds represented by Structural Formula (I) and (II), wherein Z is represented by Structural Formulas (VIII) and (XIII)-(XVI) and wherein V is W_a.

The reduction of the cyano group to an amine in Figure 3 can be carried out using metal hydrides or by catalytic reduction processes. Suitable reducing agents include lithium aluminum hydride (LAH), diisobutyl aluminum hydride (DIBAL-H), borane-methyl sulfide complex or sodium borohydride. The reduction can be carried out in an inert solvent such as ether, tetrahydrofuran (THF), methylene chloride or methanol at -78°C up to the reflux temperature for 5 minutes to 72 h. It is also possible to isolate the corresponding imine intermediate, which can be converted to the amine using similar reduction processes.

Figure 4 is a schematic showing the preparation of compounds represented by Structural Formulas (I) and (II), wherein Z is represented by Structural Formula (IV), wherein W is H. The reduction of the double bond in step 1 of Figure 4 can be carried out using the catalytic reduction process. Suitable catalyst include palladium-carbon, platinum oxide or Ranney-nickel. The reduction can be carried out in an inert solvent such as methanol, ethanol or acetic acid at temperatures of 0 to 70°C under a hydrogen pressure of 1 to 100 atm for 5 minuets to 72 h. The alkylation reactions in step 2 of Figure 4 can be carried out using the same reactants and conditions as those in step 5 of Figure 1.

Figure 5 is a schematic showing the preparation of compounds represented by Structural Formulas (I) and (II), wherein Z is represented by Structural Formula (IV), wherein W is H. The alkylation reaction in step 1 of Figure 5 can be carried out using the same reactants and conditions as those in step 5 of Figure 1. The reduction of the double bond in step 2 of Figure 5 can be carried out using the same reactants and conditions as those in step 1 of Figure 4.

Figure 7 shows the preparation of compounds represented by Structural Formula (I), where in Z is represented by Structural Formulas (VI) and wherein Ring A and/or Ring B in Z is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, u is one. In Figure 7, the alkylation reaction may be carried out in a solvent such as acetone, methyl ethyl ketone, ethyl acetate, toluene, tetrahydrofuran (THF) or dimethylformamide (DMF) in the presence of a base such as potassium carbonate or sodium hydride and a catalyst such as an alkali metal iodide at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h.

Figure 8 shows the preparation of compounds represented by Structural Formula (I), wherein Z is represented by Structural Formulas (VI) and wherein Ring A or Ring B in Z is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, u is zero. L4 is a suitable leaving group such as halogen or trifluoromethylsulfonate. In Figure 8, a palladium coupling reaction such as Stille coupling, Suzuki coupling, Heck reaction, or carboxylation using carbon monoxide can be carried out using a palladium catalyst such as tetrakis(triphenylphosphine)palladium, bis(triphenylphosphine)palladium chloride, and palladium

acetate in a solvent such as tetrahydrofuran (THF), 1,4-dioxane, toluene, dimethylformamide (DMF), or dimethylsufoxide (DMSO) in the presence of additive (when necessary) such as triphenylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, triethylamine, sodium bicarbonate, tetraethylammonium chloride, or lithium chloride at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h.

Although Figures 1-5 and 6-7 show the preparation of compounds in which Rings A and B are phenyl rings, analogous compounds with heteroaryl groups for Rings A and B can be prepared by using the starting materials with heteroaryl groups in the corresponding positions, which can be prepared according to methods disclosed in JP 61/152673, U.S. Patent 5089496, WO 89/10369, WO 92/20681 and WO 93/02081.

The invention is illustrated by the following examples which are not intended to be limiting in any way.

EXEMPLIFICATION

Example 1 - Preparation of 4-(4-Chlorophenyl)1-[3-(5-cyano-5H-dibenzo[a,d]cycloheptene-5-yl)propyl]piperidin-4-ol

To a solution of 5H-dibenzo[a,d]cycloheptene-5-carbonitrile (described in J. Med Chem. 1994, 37, 804-810)(500mg) in DMF (10ml) were added 60% sodium hydride (110mg) and 1-bromo-3- chloropropane (0.30ml) and the mixture was stirred at room temperature for 1 hours. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated

aqueous sodium chloride, and dried over magnesium sulfate. The solvent was distilled off under reduced pressure to give 5-(3-chloropropyl-5H-dibenzo[a,d]cycloheptene-5-carbonitrile. Without purification, to a solution obtained chloride in DMF (10ml) were added 4-(4-chlorophenyl)-4-hydroxypiperidine (650mg), potassium carbonate (950mg), and potassium iodide (50mg) and the mixture was stirred at 70°C for 24 hours. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:1) to give the titled compound (700mg). ^{1}H-NMR ($CDCl_3$) d: 1.22-1.34(2H,m), 1.60-1.80(3H,m), 1.93-1.99(2H,m), 2.16-2.28(6H,m), 2.56-2.60(2H,m), 6.98(2H,s), 7.25-7.47(10H,m), 8.00-8.03(2H,m). MS m/z: 469(M+1)

Example 2 - Preparation of 4-(4-Chlorophenyl)-1-[3-(5-cyano-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-yl)propyl]piperidin-4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-carbonitrile, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) d: 1.43-1.49(2H,m), 1.61-1.66(2H,m), 1.93-2.02(3H,m), 2.24-2.32(4H,m), 2.48-2.62(4H,m), 2.96-3.06(2H,m), 3.35-3.45(2H,m), 7.11-7.41(10H,m), 7.93-7.97(2H,m). MS m/z: 471(M+1)

Example 3 - Preparation of 4-(4-Chlorophenyl)-1-[3-(11-cyano-6,11-dihydrodibenz[b,e]oxepin-11-yl)propyl]piperidin-4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 6,11-dihydrodibenz[b,e]oxepin-11-carbonitrile, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.37-1.68(5H,m), 1.99-2.09(2H,m), 2.24-2.50(5H,m), 2.65-2.69(2H,m), 2.78-2.85(1H,m), 5.03(1H,d), 5.45(1H,d), 7.02-7.43(10H,m), 7.82-7.86(1H,m), 7.95-8.00(1H,m). MS m/z: 473(M+1)

Example 4 - Preparation of 1-[3-(11-Cyano-6,11-dihydrodibenz[b,e]oxepin-11-yl)propyl]-4-(4-fluorophenyl)piperidin-4-ol

Following the procedure of example 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-fluorophenyl)- 4-hydroxypiperidine, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.40-1.68(4H,m), 1.88-2.08(3H,m), 2.29-2.50(5H,m), 2.63-2.67(2H,m), 2.77-2.84(1H,m), 5.03(1H,d), 5.44(1H,d), 6.95-7.46(10H,m), 7.81-7.85(1H,m), 7.94-7.99(1H,m). MS m/z: 457(M+1)

Example 5 - Preparation of 4-(4-Chlorophenyl)-1-[3-(11-cyano-6,11-dihydro-2-fluorodibenz[b,e]oxepin-11-yl)propyl]piperidin- 4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 6,11-dihydro-2-fluorodibenz[b,e]oxepin-11-carbonitrile, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ:

1.37-1.69(5H,m), 1.98-2.09(2H,m), 2.25-2.48(5H,m), 2.65-2.70(2H,m), 2.78-2.87(1H,m), 5.01(1H,d), 5.42(1H,d), 6.99-7.11(3H,m), 7.25-7.43(6H,m), 7.54-7.59(1H,m), 7.92-7.95(1H,m). MS m/z: 491(M+1)

Example 6 - Preparation of 1-[3-(2-Bromo-11-cyano-6,11-dihydrodibenz[b,e]oxepin-11-yl)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 2-bromo-6,11-dihydrodibenz[b,e]oxepin-11-carbonitrile, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.37-1.69(5H,m), 1.97-2.09(2H,m), 2.24-2.48(5H,m), 2.66-2.85(3H,m), 5.00(1H,d), 5.43(1H,d), 6.97-7.02(2H,m), 7.24-7.46(7H,m), 7.91-7.95(2H,m).
MS m/z: 551, 553(M+1)

Example 7 - Preparation of 4-(4-Chlorophenyl)-1-[3-(11-cyano-6,11-dihydro-2-methyldibenz[b,e]oxepin-11-yl)propyl]piperidin-4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 6,11-dihydro-2-methyldibenz[b,e]oxepin-11-carbonitrile, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.40-1.70(5H,m), 1.98-2.09(2H,m), 2.25-2.52(8H,m), 2.68-2.73(2H,m), 2.81-2.90(1H,m), 5.00(1H,d), 5.44(1H,d), 6.98-7.43(9H,m), 7.63(1H,d), 7.94-7.98(1H,m). MS m/z: 487(M+1)

Example 8 - Preparation of 4-(4-Chlorophenyl)-1-[3-(11-cyano-3,4-dichloro-6,11-dihydro-dibenz[b,e]oxepin-11-yl)propyl]piperidin- 4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 3,4-dichloro-6,11-dihydrodibenz[b,e]oxepin-11-carbonitrile, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.40-1.71(5H,m), 2.00-2.10(2H,m), 2.28-2.50(5H,m), 2.65-2.85(3H,m), 5.04(1H,d), 5.46(1H,d), 6.99-7.03(1H,m), 7.26-7.44(7H,m), 7.91-7.95(2H,m).
MS m/z: 541(M+1)

Example 9 - Preparation of 4-(4-Chlorophenyl)-1-[3-(11-cyano- 6,11-dihydro-2,3-methylenedioxydibenz[b,e]oxepin-11-yl)propyl]piperidin-4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 6,11-dihydro-2,3-methylenedioxydibenz[b,e]oxepin-11-carbonitrile, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.60-1.90(5H,m), 2.30-2.50(2H,m), 2.80-3.30(8H,m), 5.05(1H,d), 5.45(1H,d), 6.02(2H,brd), 6.68(1H,s), 6.97-7.01(1H,m), 7.26-7.43(7H,m), 7.83-7.87(2H,m). MS m/z: 517(M+1)

Example 10 - Preparation of 4-(4-Chlorophenyl)-1-[3-(11-cyano-6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl] piperidin-4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 6,11-dihydrodibenzo[b,e]thiepin-11-carbonitrile, the titled

compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.63-1.76(5H,m), 2.03-2.16(2H,m), 2.37-2.52(4H,m), 2.72-2.85(3H,m), 3.03-3.10(1H,m), 4.10(1H,d), 4.54(1H,d), 7.13-7.44(10H,m), 7.81-7.87(2H,m). MS m/z: 489(M+1)

Example 11 - Preparation of 1-[3-(11-Cyano-6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl]-4-phenylpiperidin-4-ol

Following the procedure of example 10, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-hydroxy-4-phenylpiperidine, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.63-1.77(5H,m), 2.02-2.16(2H,m), 2.37-2.52(4H,m), 2.72-2.85(3H,m), 3.03-3.10(1H,m), 4.10(1H,d), 4.55(1H,d), 7.13-7.52(10H,m), 7.81-7.88(2H,m). MS m/z: 455(M+1)

Example 12 - Preparation of 4-(4-Bromophenyl)-1-[3-(11-cyano-6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl]piperidin-4-ol

Following the procedure of example 10, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-bromophenyl)-4- hydroxypiperidine, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.64-1.82(5H,m), 2.02-2.12(2H,m), 2.32-2.48(4H,m), 2.69-2.85(3H,m), 2.99-3.09(1H,m), 4.07(1H,d), 4.50(1H,d), 7.11-7.46(10H,m), 7.79-7.86(2H,m). MS m/z: 533, 535(M+1)

Example 13 - Preparation of 1-[3-(2-Bromo-11-cyano-6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 2-bromo-6,11-dihydrodibenzo[b,e]thiepin-11-carbonitrile, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.63-1.78(5H,m), 2.03-2.14(2H,m), 2.35-2.52(4H,m), 2.72-2.80(3H,m), 3.00-3.10(1H,m), 4.15(1H,brd), 4.50(1H,d), 7.07-7.45(10H,m), 7.73-7.81(1H,m), 7.95(1H,d). MS m/z: 567, 569(M+1)

Example 14, 15 - Preparation of 4-(4-Chlorophenyl)-1-[3-(11-cyano-6,11-dihydro-5-oxodibenzo[b,e]thiepin-11-yl)propyl]piperidin-4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 6,11-dihydro-5-oxodibenzo[b,e]thiepin-11-carbonitrile, the titled compound was prepared. The diastereomers were separated by silica gel chromatography. isomer 1 ^{1}H-NMR ($CDCl_3$) δ: 1.20-1.35(1H,m), 1.63-1.69(4H,m), 2.04-2.84(10H,m), 4.21(1H,d), 4.31(1H,d), 7.18-7.65(9H,m), 8.03-8.13(3H,m). MS m/z: 505(M+1) isomer 2 ^{1}H-NMR ($CDCl_3$) d: 1.25-1.38(1H,m), 1.65-2.15(6H,m), 2.28-2.82(8H,m), 4.65(1H,d), 4.82(1H,d), 7.27-7.56(9H,m), 7.92-8.00(3H,m). MS m/z: 505(M+1)

Example 16 - Preparation of 4-(4-Chlorophenyl)-1-[3-(11-cyano- 6,11-dihydro-5,5-dioxodibenzo[b,e]thiepin-11-yl)propyl]piperidin-4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 6,11-dihydro-5,5-dioxodibenzo[b,e]thiepin-11-carbonitrile, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.40-2.72(14H,m), 3.08-3.22(1H,m), 4.58(1H,d), 5.58(1H,d), 7.29-7.58(9H,m), 7.99-8.13(3H,m). MS m/z: 521(M+1)

Example 17 - Preparation of 4-(4-Chlorophenyl)-1-[3-(6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl]piperidin-4-ol

To a solution of 4-(4-chlorophenyl)-1-[3-(11-cyano-6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl]piperidin-4-ol (430mg) in THF (10ml) was added 1M lithium aluminum hydride THF solution (1.5ml) and the mixture was heated to reflux for 3 hours. The reaction mixture was cooled with ice, water (0.06ml), then 15% aqueous sodium hydroxide (0.06ml), then water (0.18ml) were added carefully. The granular salt was filtered off and the filtrate was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:1) to give the titled compound (280mg).
^{1}H-NMR ($CDCl_3$) δ: 1.55-1.80(4H,m), 2.03-2.16(2H,m), 2.25-2.52(6H,m), 2.72-2.80(2H,m), 3.90(1H,brs), 4.48(1H,brt), 4.68(1H,brs), 6.96-7.45(12H,m). MS m/z: 464(M+1)

Example 18 - Preparation of 4-(4-Chlorophenyl)-1-[3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-yl)propyl]piperidin-4-ol

Following the procedure of example 17, but replacing 4-(4-chlorophenyl)-1-[3-(11-cyano-6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl]piperidin-4-ol with 4-(4-chlorophenyl)-1-[3-(5-cyano-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-yl)propyl]piperidin-4-ol, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.40-1.58(2H,m), 1.62-1.71(2H,m), 1.98-2.20(4H,m), 2.30-2.42(4H,m), 2.67-2.78(2H,m), 2.95-3.08(2H,m), 3.30-3.44(2H,m), 4.01(1H,t), 7.10-7.46(12H,m). MS m/z: 446(M+1)

Example 19 - Preparation of 4-(4-Chlorophenyl)-1-[3-(6,11-dihydrodibenz[b,e]oxepin-11-yl)propyl]piperidin-4-ol

Following the procedure of example 17, but replacing 4-(4-chlorophenyl)-1-[3-(11-cyano-6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl]piperidin-4-ol with 4-(4-chlorophenyl)-1-[3-(11-cyano-6,11-dihydrodibenz[b,e]oxepin- 11-yl)propyl]piperidin-4-ol, the titled compound was prepared.

^{1}H-NMR ($CDCl_3$) δ: 1.36-1.49(2H,m), 1.58-1.67(2H,m), 1.95-2.33(8H,m), 2.63-2.68(2H,m), 3.74(1H,t), 4.95(1H,d), 5.48(1H,d), 6.95-7.39(12H,m). MS m/z: 448(M+1)

Example 20 - Preparation of 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-11-iminomethyldibenzo[b,e]thiepin-11-yl)propyl]-piperidin-4-ol

To a solution of 4-(4-chlorophenyl)-1-[3-(11-cyano-6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl]piperidin-4-ol (1.92g) in dichloromethane (30ml) at -78°C was added 1M diisobutyl aluminum hydride dichloromethane solution (10ml). The reaction mixture was warmed to room temperature, and stirred for 30 minutes. Water and dichloromethane were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate to give the titled compound (1.16g). ^{1}H-NMR ($CDCl_3$) δ: 1.65-1.80(5H,m), 2.02-2.18(2H,m), 2.45-2.60(6H,m), 2.78-2.86(2H,m), 3.82(1H,d), 4.25(1H,d), 7.05-7.45(12H,m), 8.28(1H,brs). MS m/z: 491(M+1)

Example 21 - Preparation of 1-[3-(11-aminomethyl-6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl]-4-(4-chlorophenyl)piperidin-4-ol

To a solution of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-11-iminodibenzo[b,e]thiepin-11-yl)propyl]piperidin-4-ol (600mg) in methanol (15ml) was sodium borohydride (220mg), and the mixture was stirred at room temperature for 10 hours. The solvent was distilled off under reduced pressure. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried

over magnesium sulfate. The solvent was distilled off under reduced to give the titled compound (600mg). MS m/z:493(M+1)

Example 22 - Preparation of Phenyl N-[11-[3-(4-(4-chlorophenyl)-4-hydroxypiperidino)propyl]-6,11-dihydrodibenzo[b,e]thiepin-11-yl)methyl carbamate

To a solution of 4-(4-chlorophenyl)-1-[3-(11-aminomethyl-6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl] piperidin-4-ol (610mg) in THF (20ml) was triethylamine (0.2ml) and phenyl chlorocarbonate (0.16ml) at 0°C, and the mixture was stirred for 1 hours. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate to give the titled compound (400mg). ^{1}H-NMR ($CDCl_3$) δ: 1.40-2.90(15H,m), 4.05-4.12(2H,m), 4.38(1H,d), 4.50-4.60(1H,m), 5.98(1H,brs), 6.96-7.54(17H,m). MS m/z: 613(M+1)

Example 23 - Preparation of 1-[11-[3-(4-(4-chlorophenyl)-4-hydroxypiperidino)propyl]-6,11-dihydrodibenzo[b,e]thiepin-11-yl]methyl-8-(3-hydroxypropyl)urea

To a solution phenyl N-[2-[3-[4-(4-chlorophenyl)-4-hydroxypiperidino]propyl]-2-(6,11-dihydrodibenzo[b,e]thiepin- 11-yl)ethyl] carbamate (300mg) in DMF (10ml) were added 3-amino-1-propanol (70mg), potassium carbonate (130mg) and the mixture was stirred at room temperature for 16 hours.

Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-methanol (9:1) to give the titled compound (200mg). ^{1}H-NMR ($CDCl_3$) δ: 1.40-1.70(6H,m), 2.01-2.08(2H,m), 2.30-2.63(8H,m), 3.12 (2H,q), 3.42(2H,t), 4.00-4.12(2H,m), 4.22-4.28(2H,m), 4.82(1H,brt), 4.99(1H,brs), 6.98-7.45(12H,m).MS m/z: 594(M+1)

Example 24 - Preparation of 4-(4-Chlorophenyl)-1-[3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-yl)-3-propioyl]piperidin-4-ol

To a solution 10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-carbonitrile (500mg) in THF (5ml) was added 1.6M n-butyl lithium hexane solution (1.8ml) at 0°C. The mixture was warmed to room temperature, and stirred for 20 minutes. To the reaction mixture cooled to 0°C was added ethyl 3-(4-(4-chlorophenyl)-4-hydroxypiperidine-1-yl)propionate (310mg) dropwise as THF solution (2ml), and the mixture was warmed to room temperature, and stirred for 30 minutes. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:1) to give the titled compound (380mg). ^{1}H-NMR ($CDCl_3$) δ: 1.57-1.62(2H,m),

1.91-2.01(3H,m), 2.27-2.84(10H,m), 3.30-3.44(2H,m), 4.65(1H,s), 7.10-7.38(12H,m).
MS m/z: 460(M+1)

Examples 28 - 59 can be prepared by methods set forth in the schemes in Figure 1-5 and the procedures described above.

Example 60 - Membrane Preparations for Chemokine Binding and Binding Assays

Membranes were prepared from THP-1 cells (ATCC #TIB202). Cells were harvested by centrifugation, washed twice with PBS (phosphate-buffered saline), and the cell pellets were frozen at -70 to -85°C. The frozen pellet was thawed in ice-cold lysis buffer consisting of 5 mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethane-sulfonic acid) pH 7.5, 2 mM EDTA (ethylenediaminetetraacetic acid), 5 μg/ml each aprotinin, leupeptin, and chymostatin (protease inhibitors), and 100 μg/ml PMSF (phenyl methane sulfonyl fluoride - also a protease inhibitor), at a concentration of 1 to 5 x 10^7 cells/ml. This procedure results in cell lysis. The suspension was mixed well to resuspend all of the frozen cell pellet. Nuclei and cell debris were removed by centrifugation of 400 x g for 10 minutes at 4°C. The supernatant was transferred to a fresh tube and the membrane fragments were collected by centrifugation at 25,000 x g for 30 minutes at 4°C. The supernatant was aspirated and the pellet was resuspended in freezing buffer consisting of 10 mM HEPES pH 7.5, 300 mM sucrose, 1μg/ml each aprotinin, leupeptin, and chymostatin, and 10 μg/ml

PMSF (approximately 0.1 ml per each 10^8 cells). All clumps were resolved using a minihomogenizer, and the total protein concentration was determined using a protein assay kit (Bio-Rad, Hercules, CA, cat #500-0002). The membrane solution was then aliquoted and frozen at -70 to -85°C until needed.

Binding Assays utilized the membranes described above. Membrane protein (2 to 20 μg total membrane protein) was incubated with 0.1 to 0.2 nM ^{125}I-labeled RANTES or MIP-1α with or without unlabeled competitor (RANTES or MIP-1α) or various concentrations of compounds. The binding reactions were performed in 60 to 100 μl of a binding buffer consisting of 10 mM HEPES pH 7.2, 1 mM $CaCl_2$, 5 mM $MgCl_2$, and 0.5% BSA (bovine serum albumin), for 60 min at room temperature. The binding reactions were terminated by harvesting the membranes by rapid filtration through glass fiber filters (GF/B or GF/C, Packard) which were presoaked in 0.3% polyethyleneimine. The filters were rinsed with approximately 600 μl of binding buffer containing 0.5 M NaCl, dried, and the amount of bound radioactivity was determined by scintillation counting in a Topcount beta-plate counter.

The activities of test compounds are reported in the Table below as IC_{50} values or the inhibitor concentration required for 50% inhibition of specific binding in receptor binding assays using ^{125}I-RANTES or ^{125}MIP-1α as ligand and THP-1 cell membranes. Specific binding is defined as the total binding minus the non-specific binding; non-specific

binding is the amount of cpm still detected in the presence of excess unlabeled RANTES or ^{125}MIP-1α.

Table

BIOLOGICAL DATA

Example	IC_{50} (μM)
1	<1
2	<1
3	<1
4	<1
5	<1
6	<1
7	<1
10	<1
11	<100
12	<1
13	<1
14	<1
15	<1
16	<1
17	<1
18	<1
19	<1
22	<1
23	<10
24	<1
25	<1
26	<1
27	<1

Examples 61 can be prepared by methods set forth in the schemes in Figure 1-5 and the procedures described above.

Example 62 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-propyl]piperidin-4-ol

Step 1

To a solution of 5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-one (5.0g) in THF (50ml) was added 1.1M cyclopropylmagnesium bromide THF solution (25ml) at 0°C. The reaction mixture was warmed to room temperature, and stirred for 30 minutes. Aqueous ammonium chloride and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was filtered and washed with ethyl acetate-hexane (1: 2) to give 5-cyclopropyl-5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-ol (5.0g).

Step 2

To a solution of the product of step 1 (4.3g) in acetic acid (30ml) was added 48% aqueous HBr (25ml) at 10°C. The reaction mixture was warmed to room temperature, and stirred for 12 hours. Water and ethyl acetate were added to the reaction mixture and neutralized with dilute NaOH solution. The organic layer was separated and washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:4) to

give 5-(3-bromopropylidene)-5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepine (5.6g).

^{1}H-NMR ($CDCl_3$) δ: 2.74(2H,q), 3.46(2H,t), 3.78(3H,s), 5.25(2H,brs), 6.07(1H,t), 6.72-6.82(3H,m), 7.21-7.42(5H,m), 7.56(1H,dd), 8.45(1H,dd).

Step 3

To a solution of the product of step 2 (160mg) in ethanol (3ml) and acetic acid (1ml) were added 10% Pd-C (79mg) was stirred under hydrogen (under a balloon) at room temperature for 24 hour. The mixture was filtered through the celite and distilled off under reduced pressure. The residue was purified by preparative thin layer chromatography eluting with ethyl acetate-hexane (1:2) to give 5-(3-bromopropyl)-5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepine (48mg).

^{1}H-NMR ($CDCl_3$) δ: 1.80-2.45(4H,m), 3.33-3.39(2H,m), 3.59(1h,dd), 3.77(3H,s), 4.98(1H,d), 5.44(1H,d), 6.70-6.79(2H,m), 7.08-7.14(5H,m), 7.52(1H,dd), 8.41(1H,dd).

Step 4

To a solution the product of step 3 (45mg) in DMF (1ml) were added 4-(4-chlorophenyl)-4-hydroxypiperidine (54mg) and potassium carbonate (19mg) and the mixture was stirred at 50°C for 1 hour. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was

purified by silica gel chromatography eluting with ethyl acetate-methanol (10:1) to give the titled compound (19mg).
^{1}H-NMR ($CDCl_3$) δ: 1.50(1H,brs), 1.67-1.72(2H,m), 2.00-2.47(10H,m), 2.76-2.81(2H,m), 3.59(1H,dd), 3.77(3H,s), 4.97(1H,d), 5.43(1H,d), 6.72-6.78(2H,m), 7.06-7.13(2H,m), 7.26-7.44(4H,m), 7.52(1H,dd), 8.37(1H,dd).
MS m/z: 479(M+1)

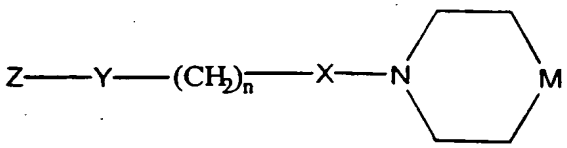
Examples 63 - 312 can be prepared by methods set forth in the schemes in Figure 1-5 and 6-7 and the procedures described above.

Those skilled in the art will be able to recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS

What is claimed is:

1. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation comprising administering to a subject an effective amount of a compound represented by the following structural formula:



;

and physiologically acceptable salts thereof, wherein:

Y is a covalent bond;

n is an integer from one to about four;

X is a covalent bond; and

M is $>NR^2$ or $>CR^1R^2$;

R^1 is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -CN, -COOH, $-CO-NR^3R^4$ or $-NR^3R^4$;

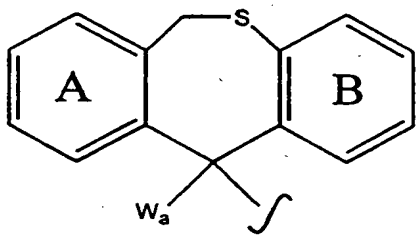
R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl

group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by the following structural formula:



;

wherein:

Ring A and Ring B are independently substituted or unsubstituted;

W_a is $-CH_2-NR^{11}R^{12}$, -CH=NH, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$; and

R^{11} and R^{12} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{11} and R^{12}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

2. The method of Claim 1 wherein Ring A or Ring B is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

t is an integer from zero to about 3; and

R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

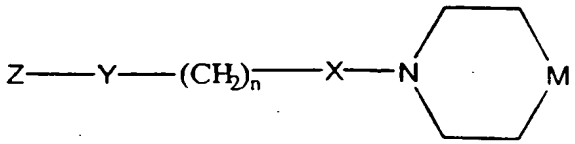
R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

3. The method of Claim 1 wherein R^1 is -OH.

4. The method of Claim 3 wherein M is $>C(OH)R^2$ and n is three.

5. The method of Claim 4 wherein R^2 is a substituted or unsubstituted aromatic group.

6. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation comprising administering to a subject in need thereof an effective amount of a compound represented by the following structural formula:



;

and physiologically acceptable salts thereof, wherein:

Y is a covalent bond;

n is an integer from one to about four;

X is a covalent bond; and

M is $>NR^2$ or $>CR^1R^2$;

R^1 is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -CN, -COOH, $-CO-NR^3R^4$ or $-NR^3R^4$;

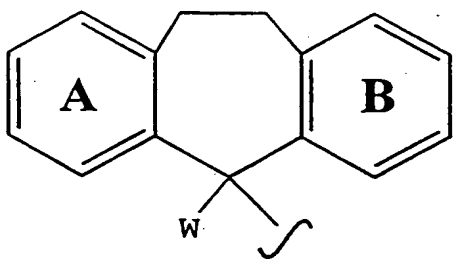
R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a

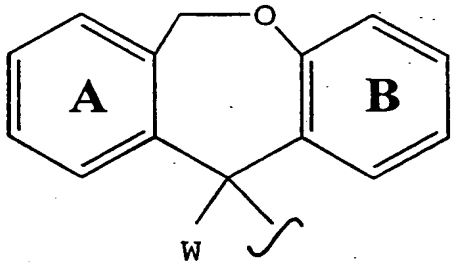
substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by a structural formula selected from:



or



;

wherein W is -H or an electron withdrawing group and Ring A and Ring B are independently substituted or unsubstituted.

7. The method of Claim 6 wherein Ring A or Ring B is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

t is an integer from zero to about 3; and

R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic

group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

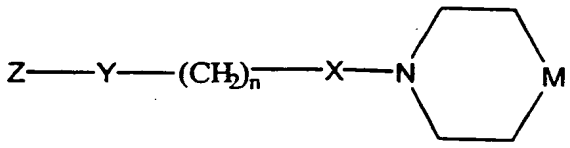
8. The method of Claim 6 wherein W is -H or -CN.

9. The method of Claim 8 wherein R^1 is -OH.

10. The method of Claim 9 wherein M is $>C(OH)R^2$ and n is three.

11. The method of Claim 10 wherein R^2 is a substituted or unsubstituted aromatic group.

12. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation comprising administering to a subject in need thereof an effective amount of a compound represented by the following structural formula:



;

and physiologically acceptable salts thereof, wherein:

Y is a covalent bond;

n is an integer from one to about five;

t is an integer from zero to about 3; and

R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

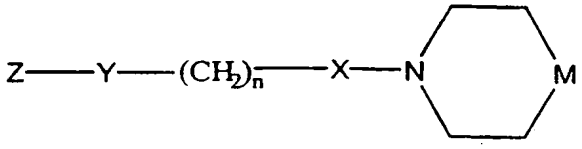
R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

14. The method of Claim 12 wherein R^1 is -OH.

15. The method of Claim 14 wherein M is $>C(OH)R^2$ and n is three.

16. The method of Claim 19 wherein R^2 is a substituted or unsubstituted aromatic group.

17. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation comprising administering to subject in need thereof an effective amount of a compound represented by the following structural formula:



;

and physiologically acceptable salts thereof, wherein:

Y is a covalent bond;

n is an integer from one to about five;

X is a covalent bond; and

M is $>NR^2$ or $>CR^1R^2$;

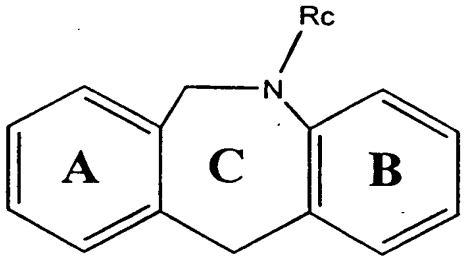
R^1 is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -CN, -COOH, $-CO-NR^3R^4$ or $-NR^3R^4$;

R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by a structural formula selected from:



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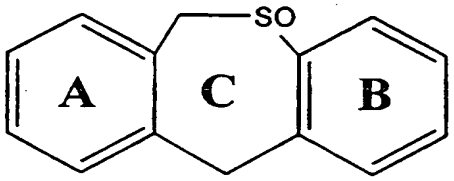

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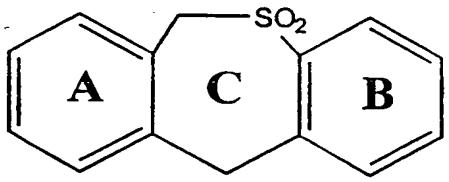

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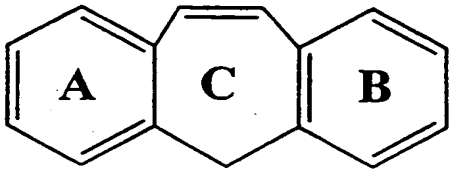
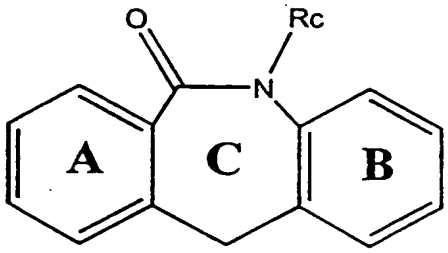


or



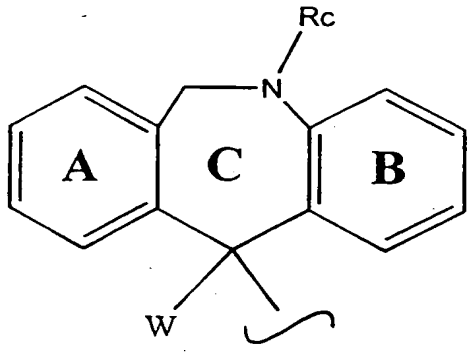
;

wherein:

Rings A, B and C are independently substituted or unsubstituted; and

R_c is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group.

18. The method of Claim 17 wherein Z is represented by a structural formula selected from:



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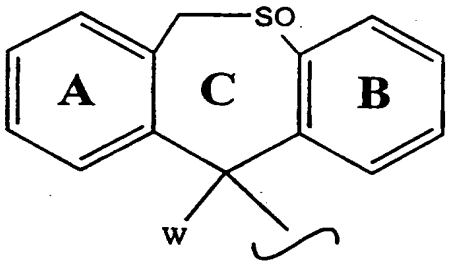

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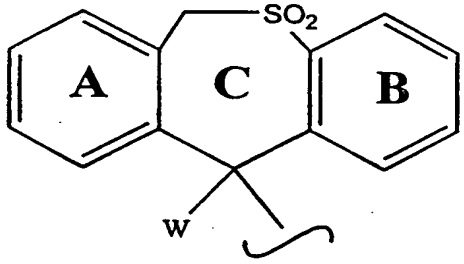

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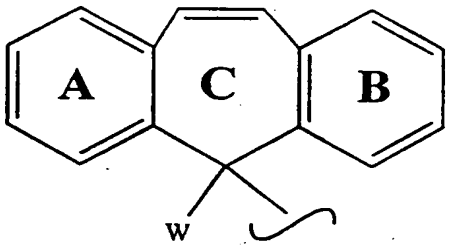
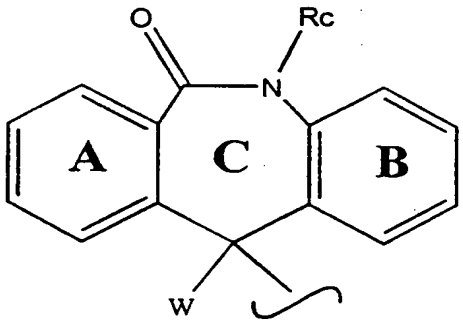


or



;

wherein W is an electron withdrawing group.

19. The method of Claim 18 wherein Ring A or Ring B is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$

$-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

t is an integer from zero to about 3;

R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

20. The method of Claim 18 wherein R_c is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{20}$; wherein:

s is an integer from one to about three;

R^{30}, R^{31} or R^{32} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{31} and R^{32}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

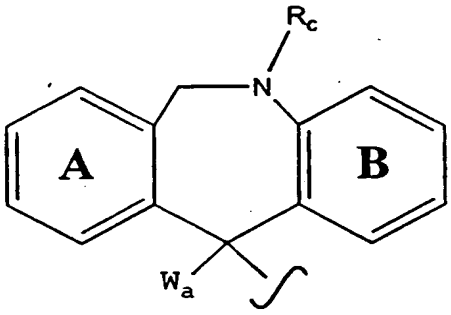
21. The method of Claim 18 wherein W is -H or -CN.

22. The method of Claim 21 wherein R^1 is -OH.

23. The method of Claim 22 wherein M is $>C(OH)R^2$ and n is three.

24. The method of Claim 23 wherein R^2 is a substituted or unsubstituted aromatic group.

25. The method of Claim 17 wherein Z is represented by a structural formula selected from:



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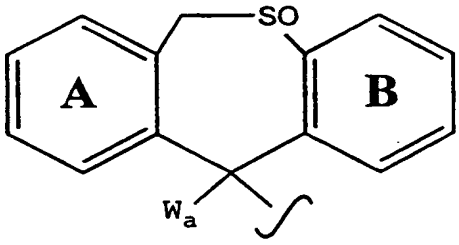

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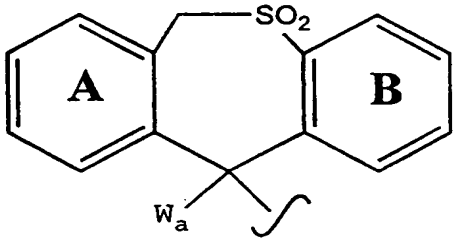
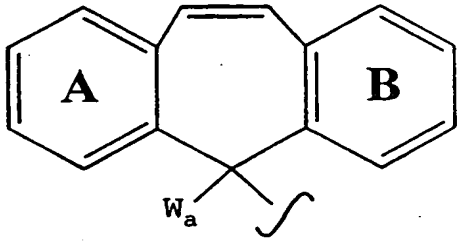
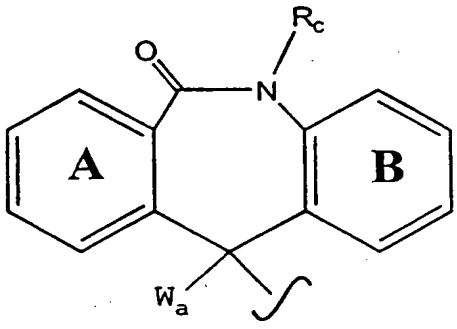


,



or



;

wherein W_a is $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, -CH=NH, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$; wherein:

R^{11} and R^{12} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{11} and R^{12}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

26. The method of Claim 25 wherein Ring A or Ring B is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

t is an integer from zero to about 3;

R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

27. The method of Claim 25 wherein R_c is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$; wherein:

s is an integer from one to about three;

R^{30}, R^{31} or R^{32} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic

group, a substituted aromatic group or a non-aromatic heterocyclic group; or

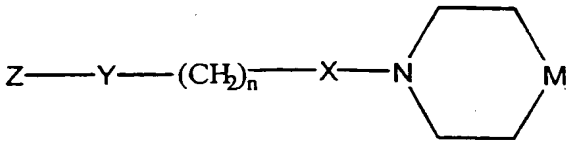
R^{31} and R^{32}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

28. The method of Claim 25 wherein R^1 is -OH.

29. The method of Claim 28 wherein M is $>C(OH)R^2$ and n is three.

30. The method of Claim 29 wherein R^2 is a substituted or unsubstituted aromatic group.

31. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation comprising administering to a subject in need thereof an effective amount of a compound represented by the following structural formula:



;

and physiologically acceptable salts thereof, wherein:

Y is a covalent bond;

n is an integer from one to about five;

X is a covalent bond; and

M is $>NR^2$ or $>CR^1R^2$;

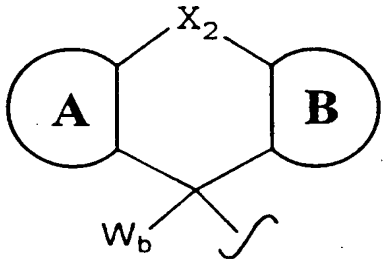
R^1 is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -CN, -COOH, -CO-NR^3R^4 or -NR^3R^4;

R^2 is -H, -OH, an acyl group, a substituted acyl group, -NR^5R^6, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by a structural formula selected from:



wherein:

Ring A is a substituted or unsubstituted heteroaryl group;

Ring B is a substituted or unsubstituted aromatic carbocyclic or heteroaryl group;

X_2 is $-S-CH_2-$, $-CH_2-S-$, $-CH_2-O-$, $-O-CH_2-$, $-CO-NR_c-$, $-NR_c-CO-$, $-CH_2-S(O)_2-$, $-S(O)_2-CH_2-$, $-CH_2-NR_c-$, $-NR_c-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2-SO-$, $-SO-CH_2-$;

W_b is $-H$, $-CH_2=NH$, $-CN$, $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$;

R^{11} and R^{12} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{11} and R^{12}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring; and

R_c is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group.

32. The method of Claim 31 wherein Ring A or Ring B is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

t is an integer from zero to about 3;

R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic

group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

33. The method of Claim 31 wherein R_c is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$; wherein:

s is an integer from zero to about 3;

R^{30}, R^{31} or R^{32} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{31} and R^{32}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

34. The method of Claim 31 wherein R^1 is -OH.

35. The method of Claim 34 wherein M is $>C(OH)R^2$ and n is three.

36. The method of Claim 35 R^2 is a substituted or unsubstituted aromatic group.

37. The method of Claim 35 wherein R^2 is an aromatic group substituted with halogen.

38. The method of Claim 37 wherein R^2 is a 4-chlorophenyl group.

39. The method of Claim 31 wherein Ring B is a substituted or unsubstituted heteroaryl group.

40. The method of Claim 39 wherein Ring A is a substituted or unsubstituted pyridyl group.

41. The method of Claim 31 wherein Ring A is a substituted or unsubstituted pyridyl group and Ring B is a substituted or unsubstituted aromatic carbocyclic group.

42. The method of Claim 31 wherein Ring A is a pyridyl group and Ring B is a substituted or unsubstituted phenyl group.

43. The method of Claim 42 wherein M is $>C(OH)R^2$ and n is three.

44. The method of Claim 43 wherein R^2 is an aromatic group substituted with halogen.

45. The method of Claim 44 wherein R^2 is a 4-chlorophenyl group.

46. The method of Claim 40 wherein:

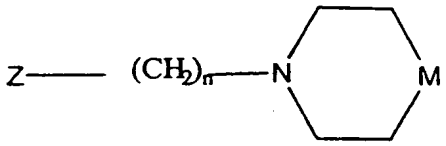
Ring B is a pyridyl group;

n is three;

M is $>C(OH)R^2$; and

R^2 is a 4-chlorophenyl group.

47. A compound represented by the following structural formula:



and physiologically acceptable salts thereof, wherein:

n is an integer from one to about five;

M is $>NR^2$ or $>CR^1R^2$;

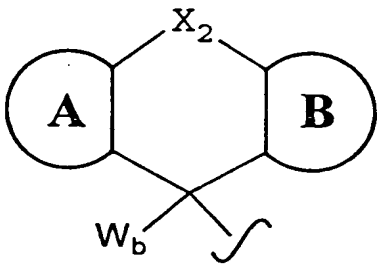
R^1 is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -CN, -COOH, $-CO-NR^3R^4$ or $-NR^3R^4$;

R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by a structural formula selected from:



wherein:

Ring A is a substituted or unsubstituted heteroaryl group;

Ring B is a substituted or unsubstituted aromatic carbocyclic or heteroaryl group;

X_2 is $-S-CH_2-$, $-CH_2-S-$, $-CH_2-O-$, $-O-CH_2-$, $-CO-NR_c-$, $-NR_c-CO-$, $-CH_2-S(O)_2-$, $-S(O)_2-CH_2-$, $-CH_2-NR_c-$, $-NR_c-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2-SO-$, $-SO-CH_2-$;

W_b is $-H$, $-CH_2=NH$, $-CN$, $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$;

R^{11} and R^{12} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{11} and R^{12}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring; and

R_c is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group.

48. The compound of Claim 47 wherein Ring A or Ring B is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

t is an integer from zero to about 3;

R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

49. The compound of Claim 47 wherein R_c is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)s-NHC(O)-O-R^{30}$; wherein:

s is an integer from one to about three;

R^{30}, R^{31} or R^{32} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{31} and R^{32}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

50. The compound of Claim 47 wherein R^1 is -OH.

51. The compound of Claim 50 wherein M is $>C(OH)R^2$ and n is three.

52. The compound of Claim 51 wherein R^2 is a substituted or unsubstituted aromatic group.

53. The compound of Claim 51 wherein R^2 is an aromatic group substituted with halogen.

54. The compound of Claim 53 wherein R^2 is a 4-chlorophenyl group.

55. The compound of Claim 47 wherein Ring B is a substituted or unsubstituted heteroaryl group.

56. The compound of Claim 55 wherein Ring A is a substituted or unsubstituted pyridyl group.

57. The compound of Claim 47 wherein Ring A is a substituted or unsubstituted pyridyl group and Ring B is a substituted or unsubstituted aromatic carbocyclic group.

58. The compound of Claim 47 wherein Ring A is a substituted or unsubstituted pyridyl group and Ring B is a substituted or unsubstituted phenyl group.

59. The compound of Claim 58 wherein M is $>C(OH)R^2$ and n is three.

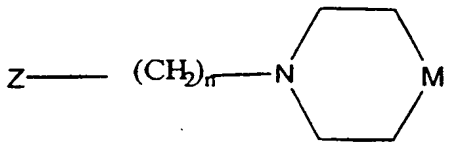
60. The compound of Claim 59 wherein R^2 is a substituted or unsubstituted aromatic group.

61. The compound of Claim 59 wherein R^2 is an aromatic group substituted with halogen.

62. The compound of Claim 61 wherein R^2 is a 4-chlorophenyl group.

63. The compound of Claim 56 wherein:
Ring B is a pyridyl group;
n is three;
M is $>C(OH)R^2$; and
R^2 is a 4-chlorophenyl group.

64. A compound represented by the following structural formula:



;

and physiologically acceptable salts thereof, wherein:

n is an integer from one to about five;

M is $>NR^2$ or $>CR^1R^2$;

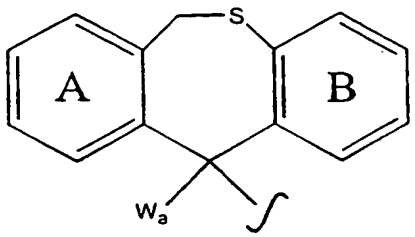
R^1 is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -CN, -COOH, $-CO-NR^3R^4$ or $-NR^3R^4$;

R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by the following structural formula:



;

W_a is $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, -CH=NH, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$;

R^{11} and R^{12} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{11} and R^{12}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring; and

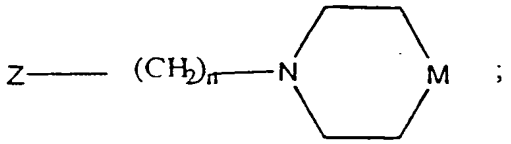
Ring A and Ring B are independently substituted or unsubstituted.

65. The compound of Claim 64 wherein R^1 is -OH.

66. The compound of Claim 64 wherein M is $>C(OH)R^2$ and n is three.

67. The compound of Claim 66 wherein R^2 is a substituted or unsubstituted aromatic group.

68. A compound represented by the following structural formula:



and physiologically acceptable salts thereof, wherein:

n is an integer from one to about five;

M is $>NR^2$ or $>CR^1R^2$;

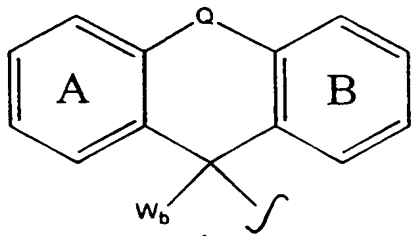
R^1 is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -CN, -COOH, $-CO-NR^3R^4$ or $-NR^3R^4$;

R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by a structural formula selected from:



;

wherein:

Q is $-CH_2-O-$, $-CH_2-NR_c-$, $-CH_2-SO-$, $-CH_2-SO_2-$, $-CH_2-CH_2-$, $-CH=CH-$ or $-CO-NR_c-$;

W_b is $-CH_2=NH$, $-CN$, $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$;

R^{11} and R^{12} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{11} and R^{12}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

Ring A and Ring B are independently substituted or unsubstituted; and

R_c is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group.

69. The compound of Claim 68 wherein Ring A or Ring B is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

t is an integer from zero to about 3;

R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

70. The compound of Claim 68 wherein R_c is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{20}$; wherein:

s is an integer from one to about three;

R^{30}, R^{31} or R^{32} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

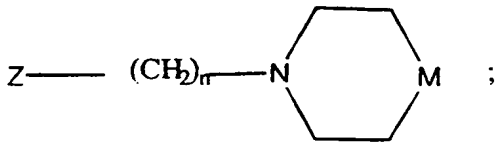
R^{31} and R^{32}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

71. The compound of Claim 68 wherein R^1 is -OH.

72. The compound of Claim 68 wherein M is $>C(OH)R^2$ and n is three.

73. The compound of Claim 72 wherein R^2 is a substituted or unsubstituted aromatic group.

74. A compound represented by the following structural formula:



;

and physiologically acceptable salts thereof, wherein:

n is an integer from one to about five;

M is $>NR^2$ or $>CR^1R^2$;

R^1 is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -CN, -COOH, $-CO-NR^3R^4$ or $-NR^3R^4$;

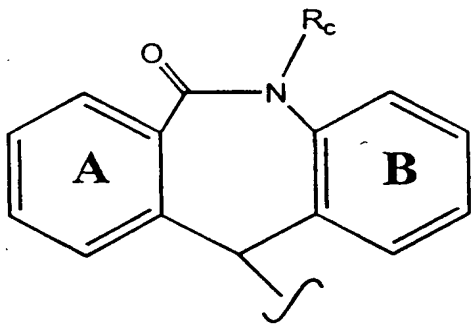
R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic

group or a substituted non-aromatic heterocyclic group; or

R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by the following structural formula:



;

R_c is a C_1-C_{20} aliphatic group, a substituted C_1-C_{20} aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

Ring A and Ring B are independently substituted or unsubstituted.

75. The compound of Claim 74 wherein Ring A or Ring B is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

t is an integer from zero to about 3;

R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

76. The compound of Claim 74 wherein R_c is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$; wherein:

s is an integer from one to about three;

R^{30}, R^{31} or R^{32} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{31} and R^{32}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

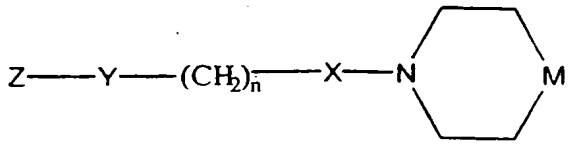
77. The compound of Claim 74 wherein R_c is an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group.

78. The compound of Claim 77 wherein R^1 is -OH.

79. The compound of Claim 78 wherein M is $>C(OH)R^2$ and n is three.

80. The compound of Claim 79 wherein R^2 is a substituted or unsubstituted aromatic group.

81. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation comprising administering to a subject in need thereof an effective amount of a compound represented by the following structural formula:



and physiologically acceptable salts thereof, wherein:

Y is a covalent bond;

n is an integer from one to about five;

X is a covalent bond; and

M is $>NR^2$ or $>CR^1R^2$;

R^1 is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -CN, -COOH, $-CO-NR^3R^4$ or $-NR^3R^4$;

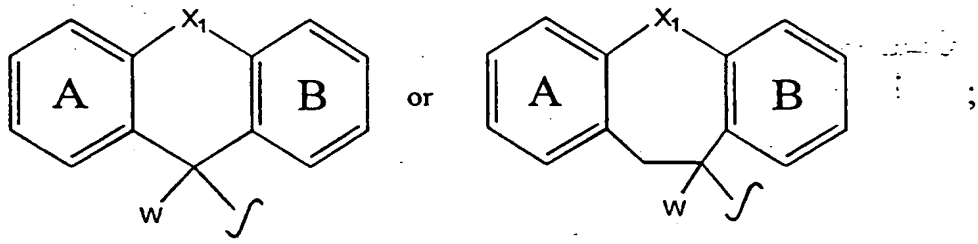
R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a

substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by the following structural formula:



;

wherein:

X_1 is a covalent bond, -S-, $-CH_2-$ or $-CH_2-S-$;

W is -H or an electron withdrawing group;

Ring A and Ring B are independently substituted or unsubstituted with the proviso that one of Ring A or Ring B is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

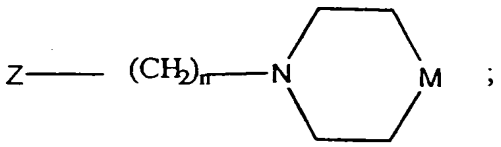
t is an integer from zero to about 3; and

R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic

group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

82. A compound represented by the following structural formula:



and physiologically acceptable salts thereof, wherein:

M is $>NR^2$ or $>CR^1R^2$;

R^1 is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -CN, -COOH, $-CO-NR^3R^4$ or $-NR^3R^4$;

R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

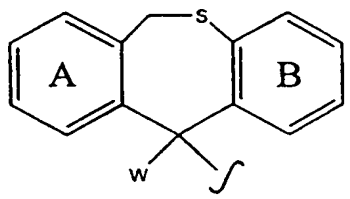
R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a

substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

n is an integer from one to about five;

Z is represented by the following structural formula:



;

W is an electron withdrawing group; and

at least one of Ring A or Ring B are independently substituted or unsubstituted and one of Ring A or Ring B is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

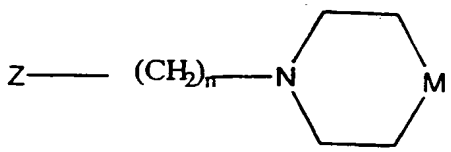
u is zero or one;

t is an integer from zero to about 3;

R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

83. A compound represented by the following structural formula:



and physiologically acceptable salts thereof, wherein:

n is an integer from one to about five;

M is $>NR^2$ or $>CR^1R^2$;

R^1 is -H, -OH, an aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -CN, -COOH, $-CO-NR^3R^4$ or $-NR^3R^4$;

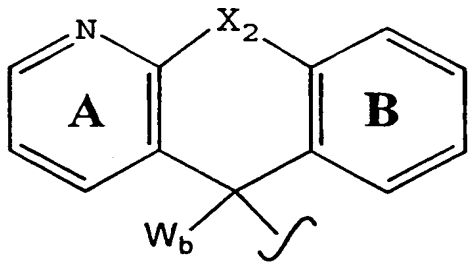
R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; wherein:

R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a

substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by a structural formula selected from:



wherein:

X_2 is $-CH_2-O-$, $-CH_2-NR_c-$, $-CH_2-SO-$, $-CH_2-SO_2-$, $-CH_2-CH_2-$, $-CH=CH-$ or $-CO-NR_c-$;

W_b is $-H$, $-CH_2=NH$, $-CN$, $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$;

R^{11} and R^{12} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{11} and R^{12}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

Ring A and Ring B are independently substituted or unsubstituted; and

R_c is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group.

84. The compound of Claim 83 wherein Ring A or Ring B is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$; wherein:

u is zero or one;

t is an integer from zero to about 3;

R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

85. The compound of Claim 83 wherein R_c is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$; wherein:

s is an integer from zero to about 3;

R^{30}, R^{31} or R^{32} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

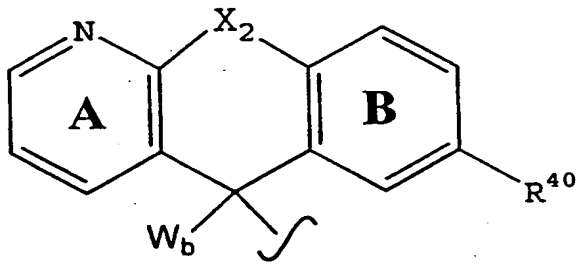
R^{31} and R^{32}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

86. The compound of Claim 83 wherein R^1 is -OH.

87. The compound of Claim 83 wherein M is $>C(OH)R^2$ and n is three.

88. The compound of Claim 87 wherein R^2 is a substituted or unsubstituted aromatic group.

89. The compound of Claim 83 wherein Ring B in Z is substituted with R^{40} para to the carbon atom in Ring B that is also bonded to X_2 in Ring C, and Z is represented by the following structural formula:



wherein:

R^{40} is -OH, halogen, aliphatic group, substituted aliphatic group, -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$;

R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

u is zero or one; and

t is an integer from zero to about 3.

90. A method of antagonizing a chemokine receptor in a mammal in need thereof comprising administering an effective amount of a compound of Claim 47 to the mammal.

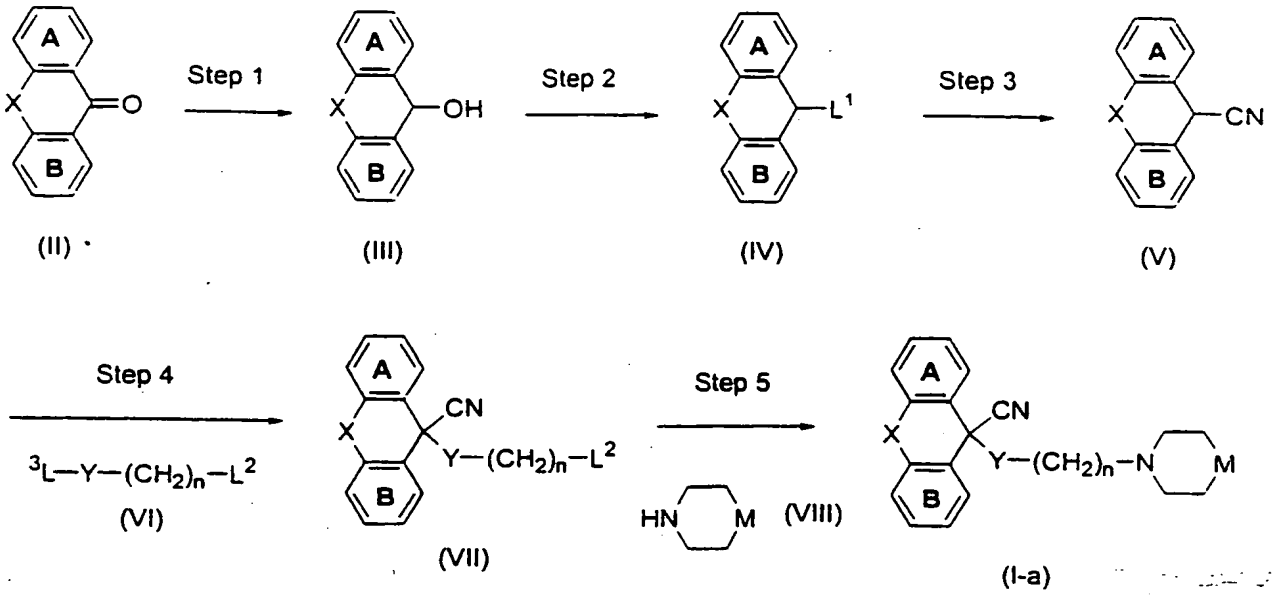
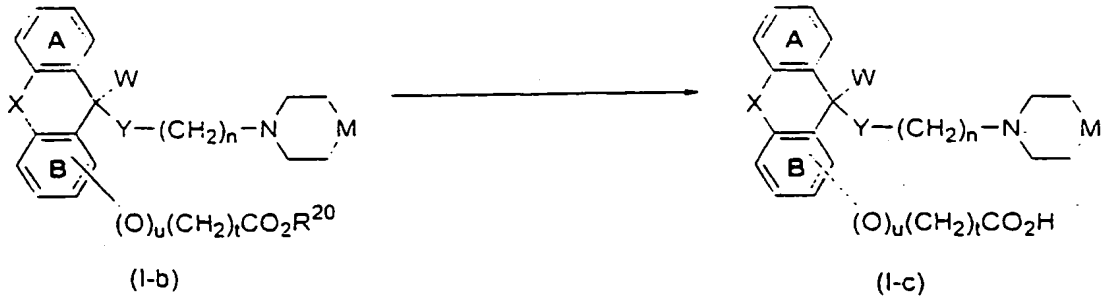

A
X
B
O
OH
L1
CN
Step 1
Step 2
Step 3
Step 4
Step 5
3L—Y—(CH2)n—L2
HN
M
(II)
(III)
(IV)
(V)
(VI)
(VII)
(VIII)
(I-a)

Figure 1


A
W
X
Y—(CH2)n—N
M
B
(O)u(CH2)tCO2R20
(I-b)
A
W
X
Y—(CH2)n—N
M
B
(O)u(CH2)tCO2H
(I-c)

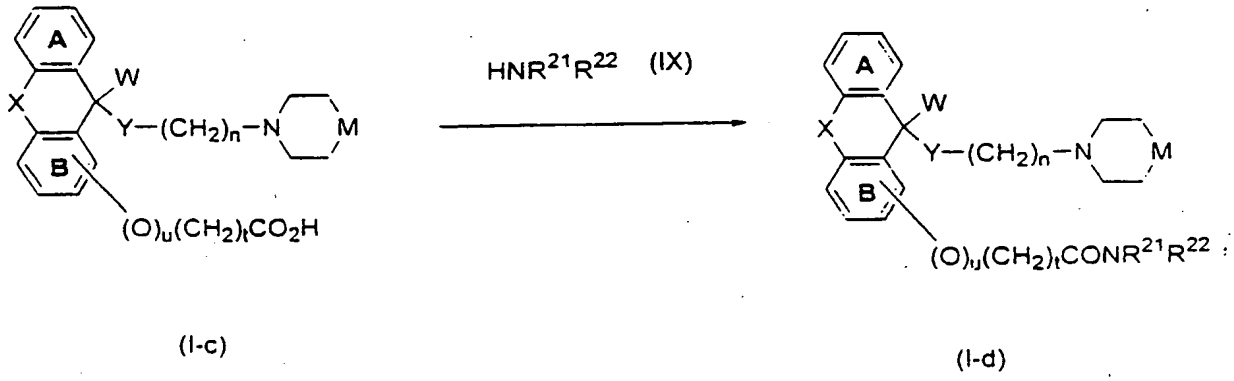
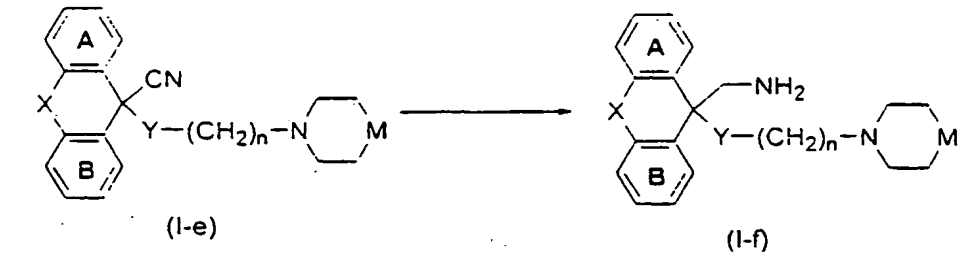
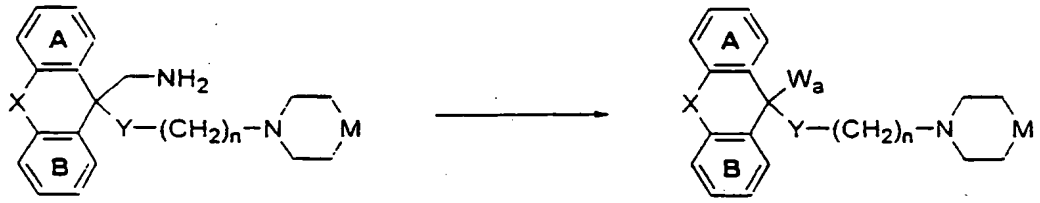

A
W
X
Y—(CH2)n—N
M
B
(O)u(CH2)tCO2H
(I-c)
HNR21R22 (IX)
A
W
X
Y—(CH2)n—N
M
B
(O)u(CH2)tCONR21R22
(I-d)

Figure 2



(I-e) (I-f)



(I-f) (I-h)

Figure 3

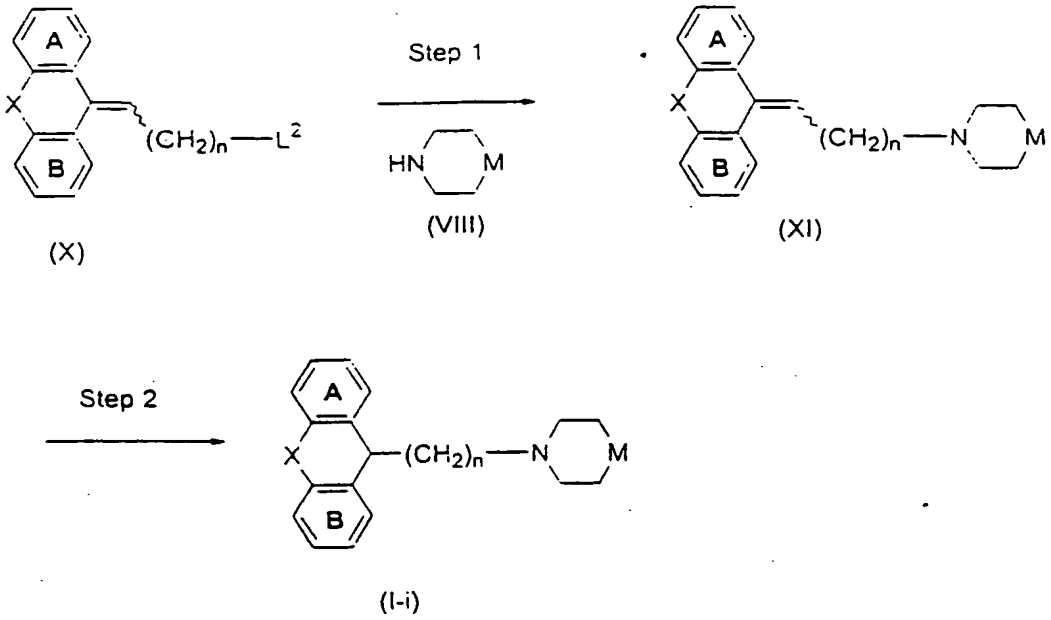


Figure 4

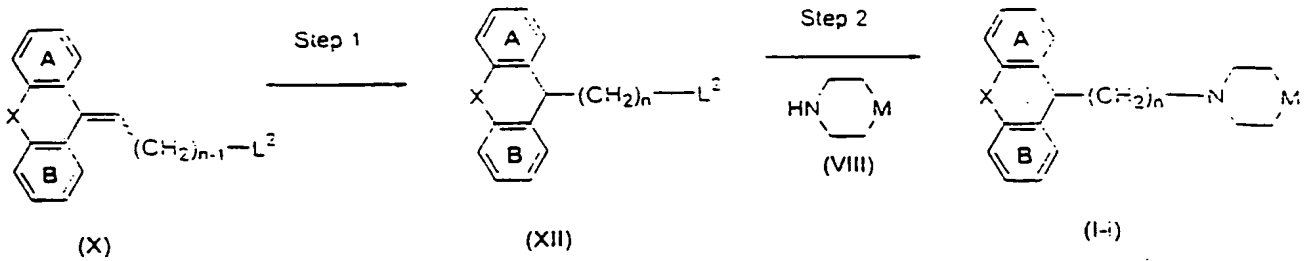
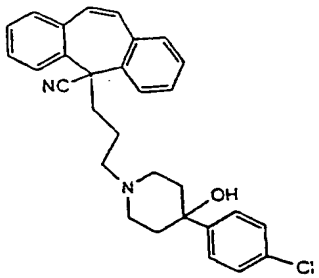
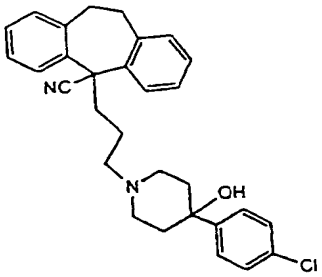


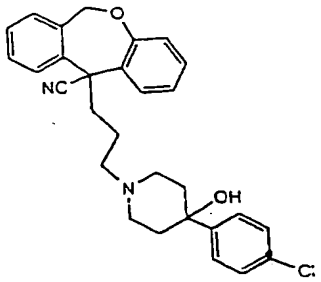
Figure 5



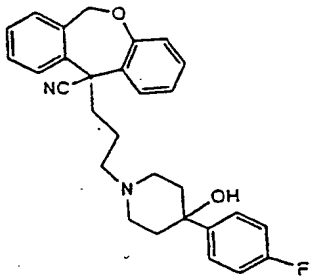
Example 1



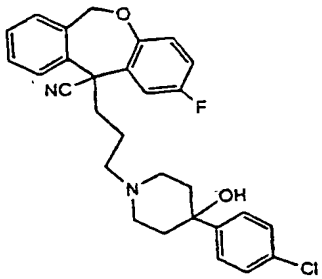
Example 2



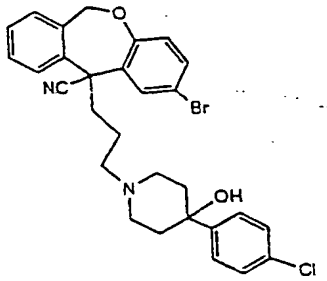
Example 3



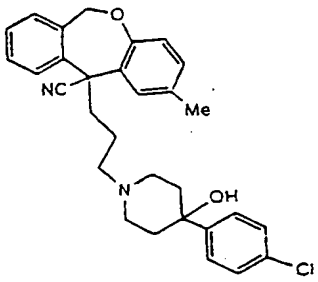
Example 4



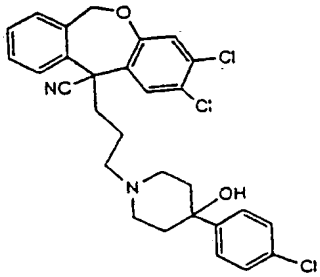
Example 5



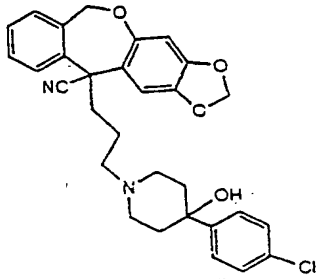
Example 6



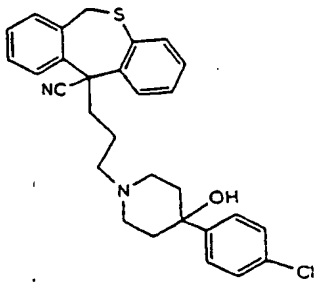
Example 7



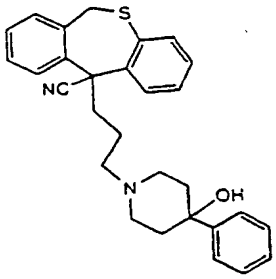
Example 8



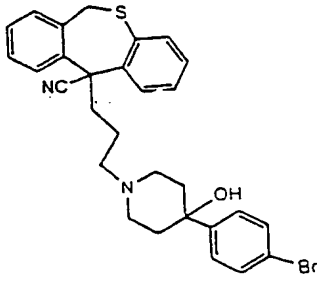
Example 9



Example 10

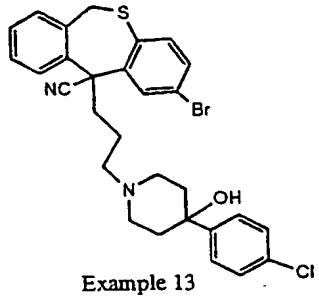


Example 11

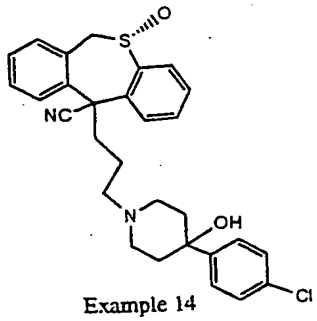


Example 12

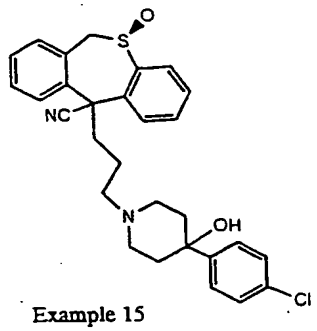
Figure 6A



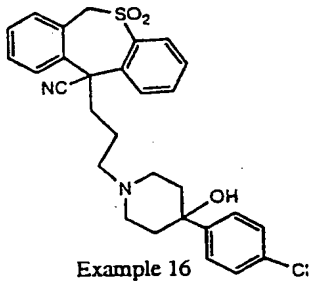
Example 13



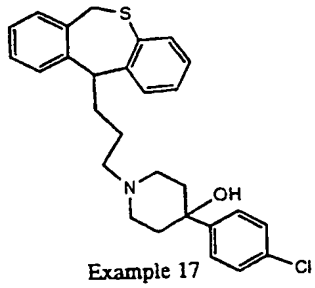
Example 14



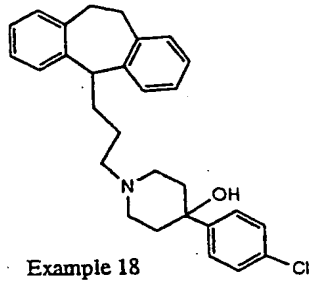
Example 15



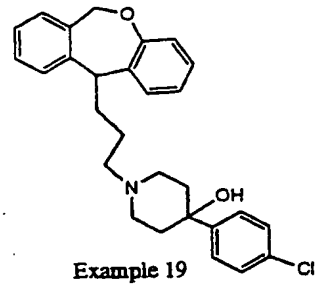
Example 16



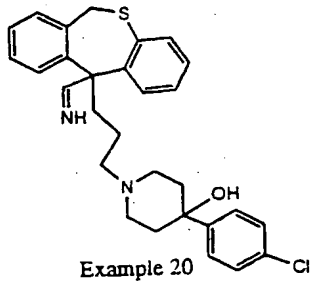
Example 17



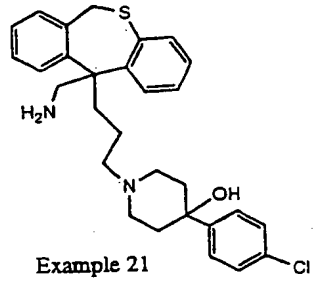
Example 18



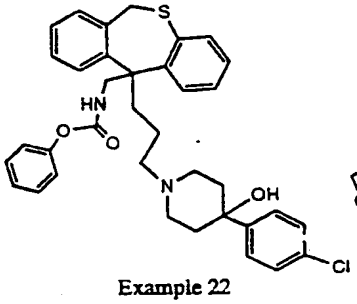
Example 19



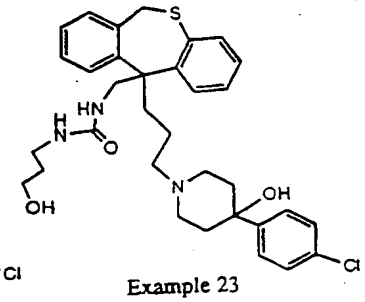
Example 20



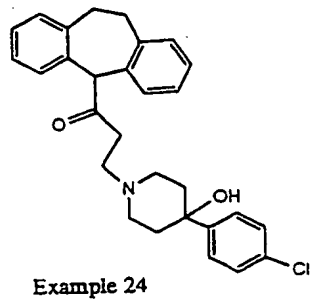
Example 21



Example 22

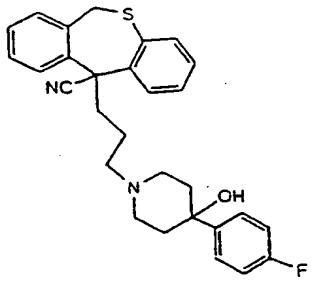


Example 23

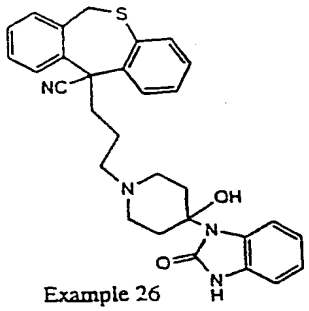


Example 24

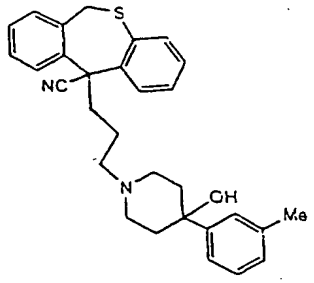
Figure 6B



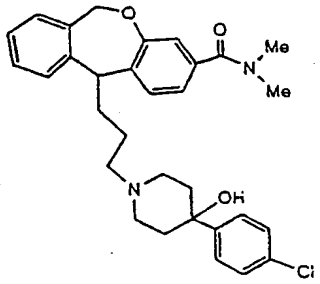
Example 25



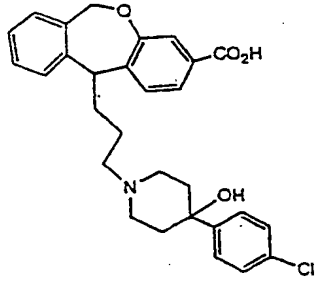
Example 26



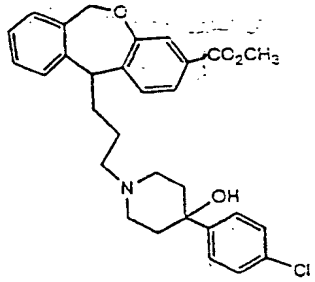
Example 27



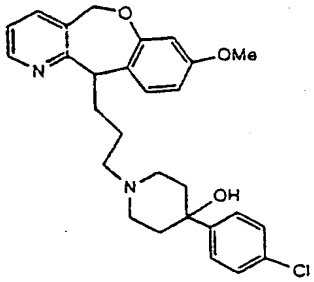
Example 28



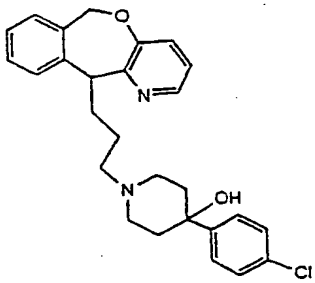
Example 29



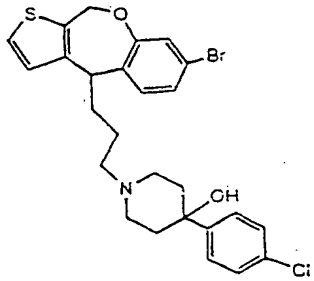
Example 30



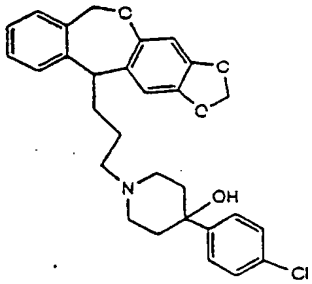
Example 31



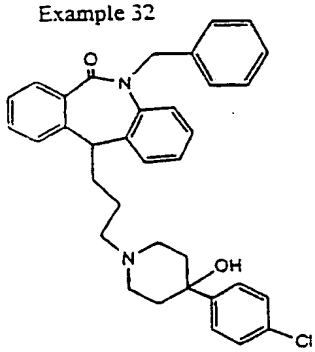
Example 32



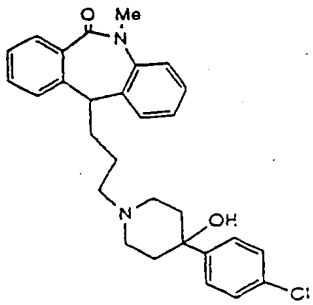
Example 33



Example 34

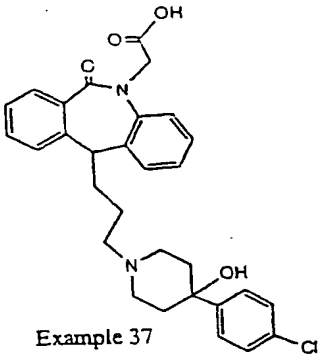


Example 35

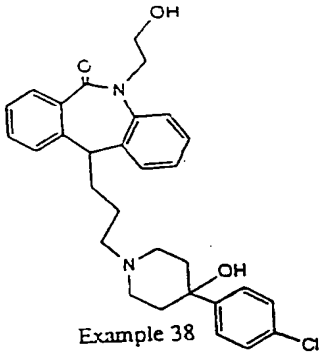


Example 36

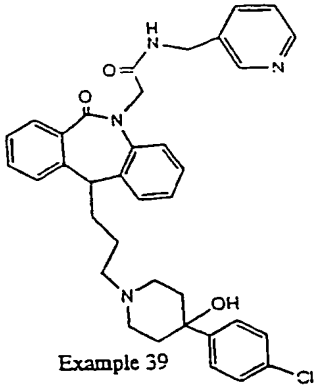
Figure 6C



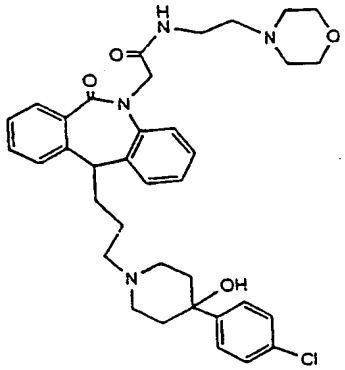
Example 37



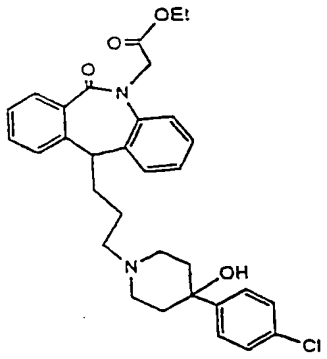
Example 38



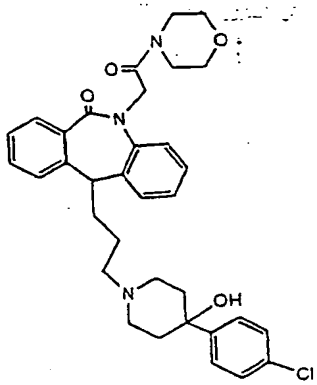
Example 39



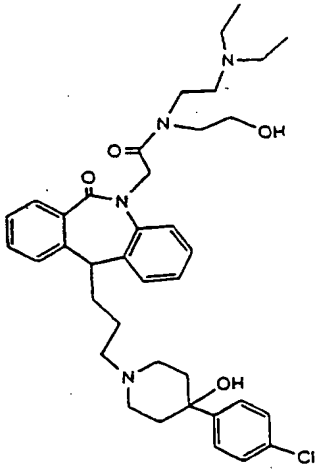
Example 40



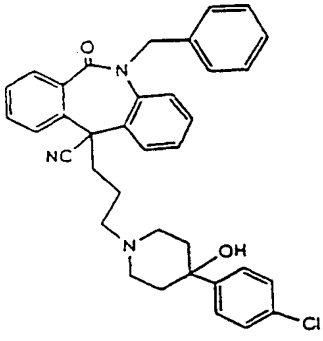
Example 41



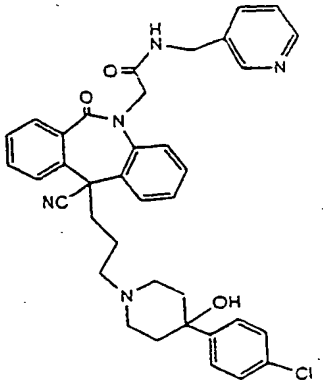
Example 42



Example 43

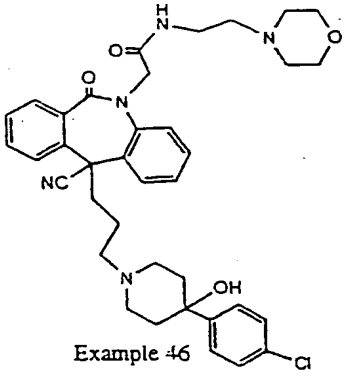


Example 44

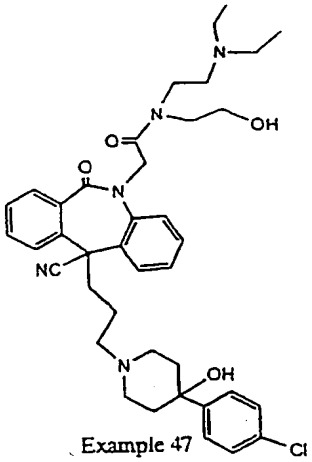


Example 45

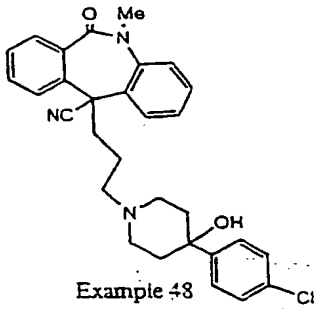
Figure 6D



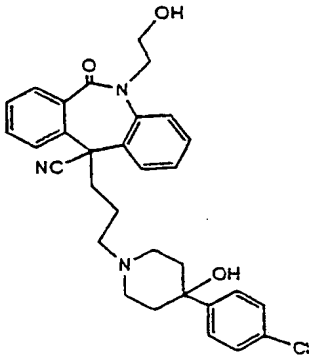
Example 46



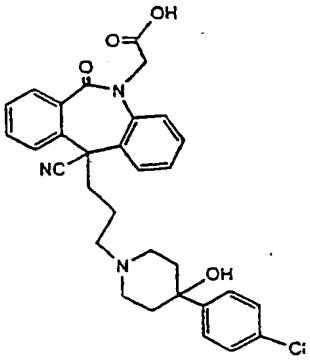
Example 47



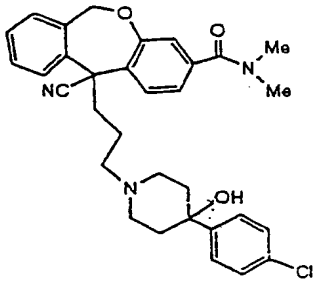
Example 48



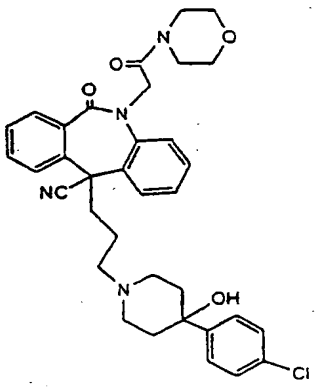
Example 49



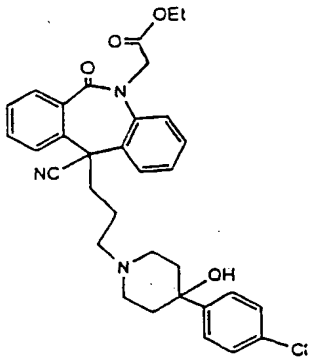
Example 50



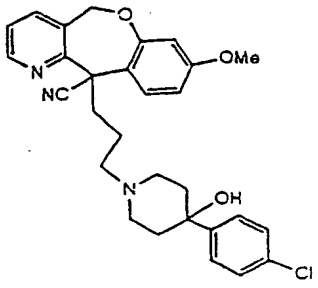
Example 51



Example 52

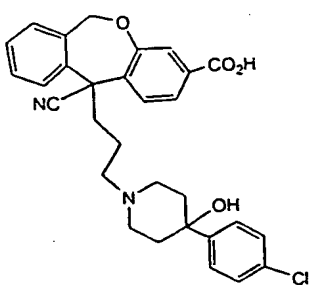


Example 53

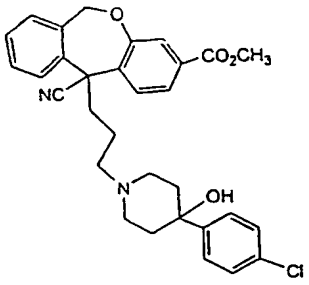


Example 54

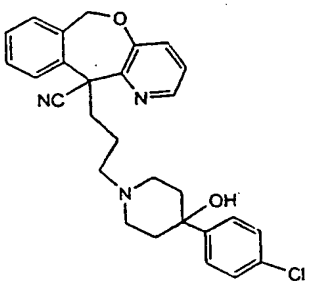
Figure 6E



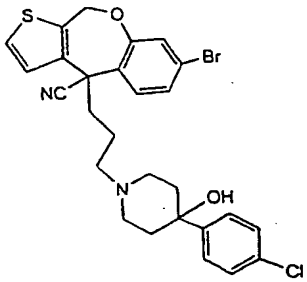
Example 55



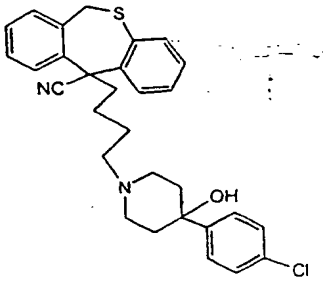
Example 56



Example 57

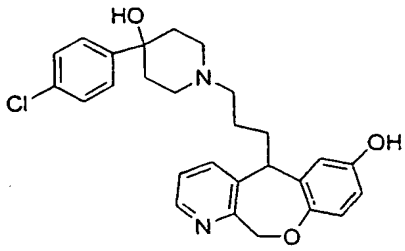


Example 58

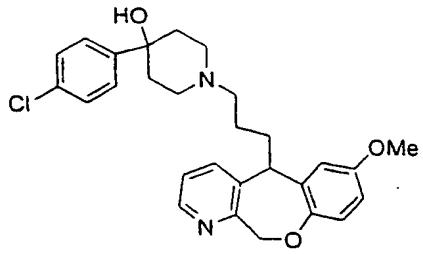


Example 59

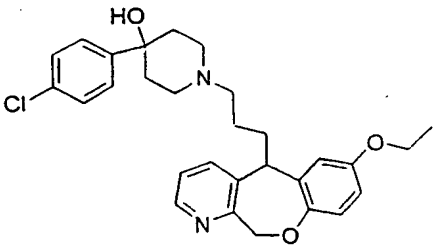
Figure 6F



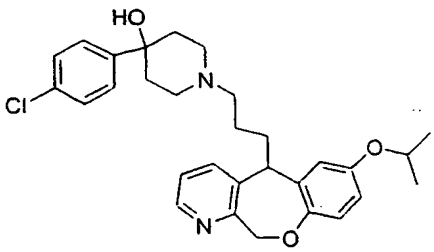
Example 61



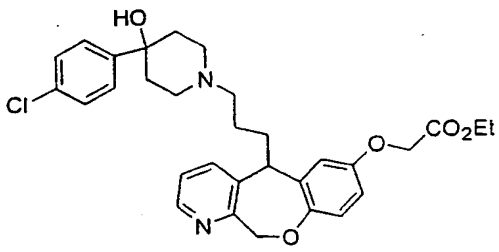
Example 62



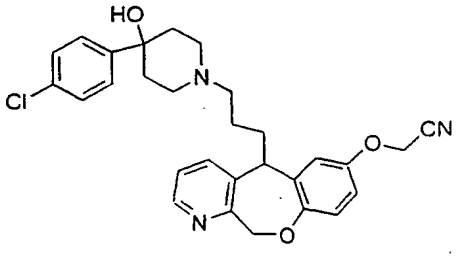
Example 63



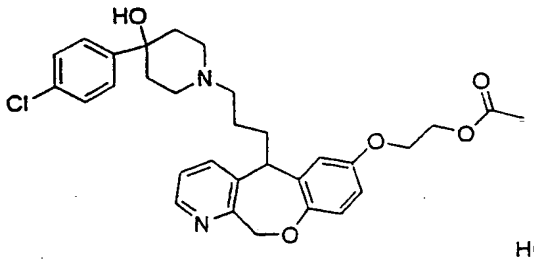
Example 64



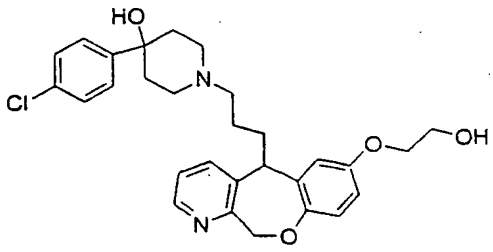
Example 65



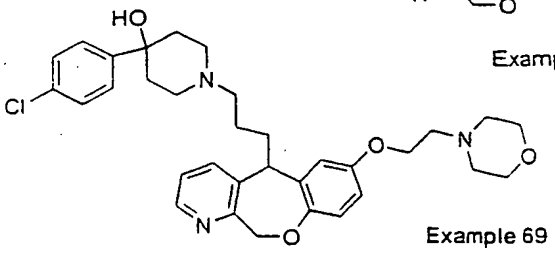
Example 66



Example 67

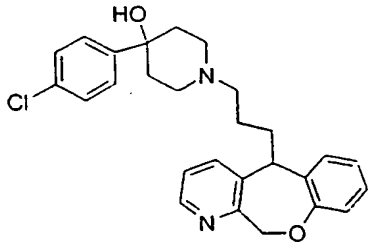


Example 68

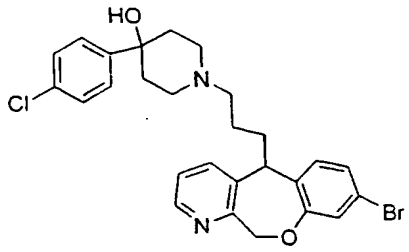


Example 69

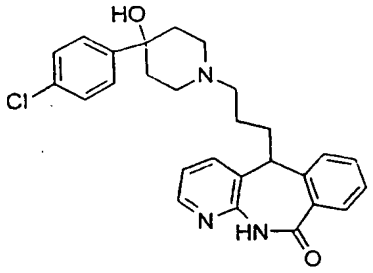
Figure 6G



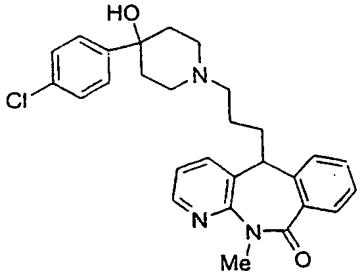
Example 70



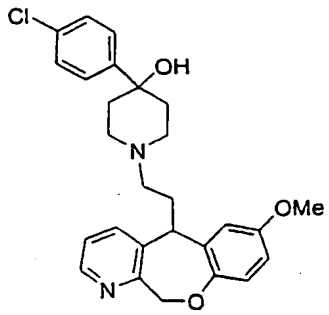
Example 71



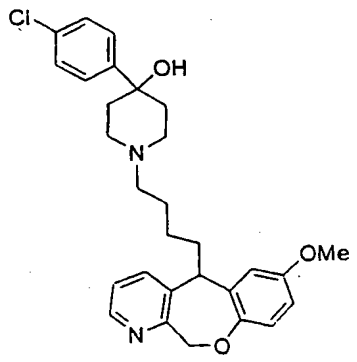
Example 72



Example 73

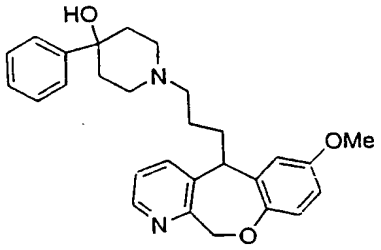


Example 74

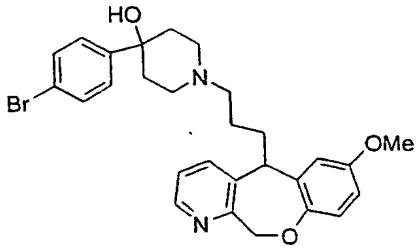


Example 75

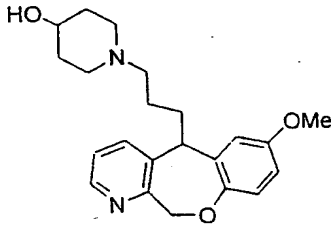
Figure 6H



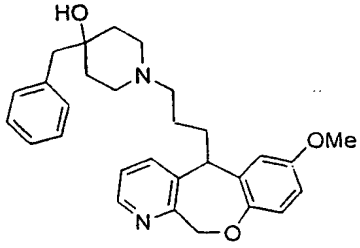
Example 76



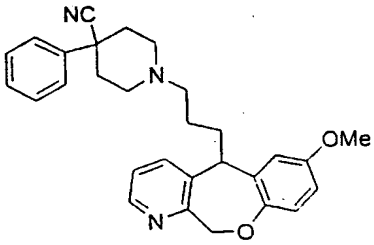
Example 77



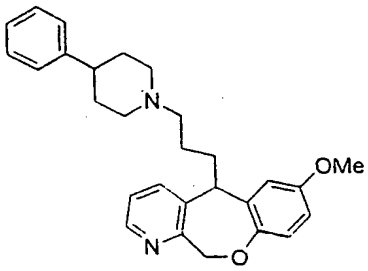
Example 78



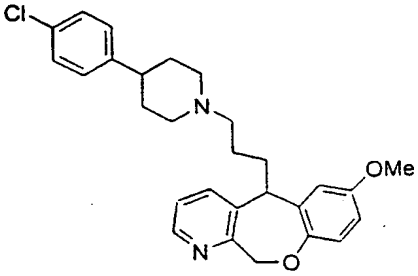
Example 79



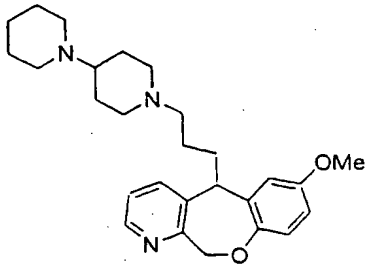
Example 80



Example 81

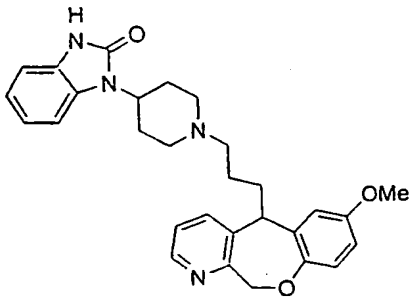


Example 82

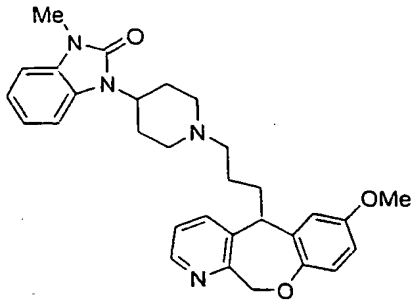


Example 83

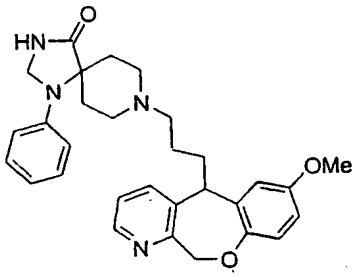
Figure 6I



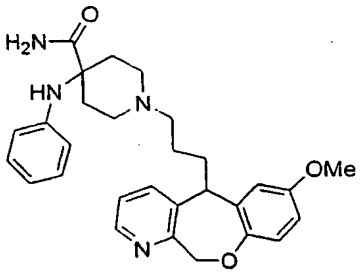
Example 84



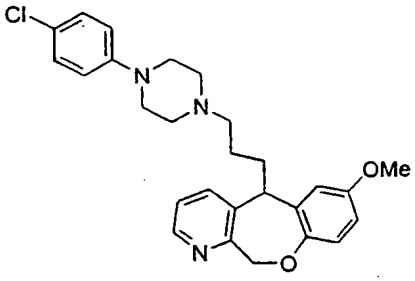
Example 85



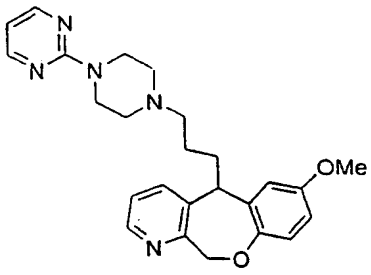
Example 86



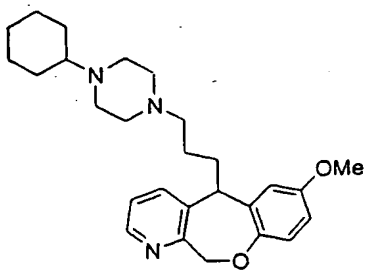
Example 87



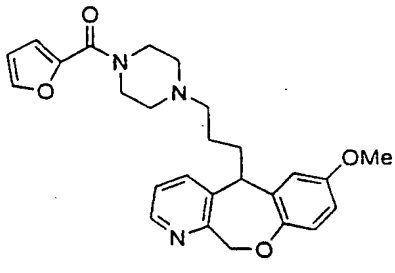
Example 88



Example 89

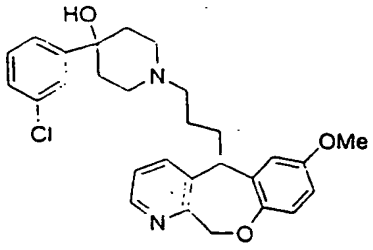


Example 90

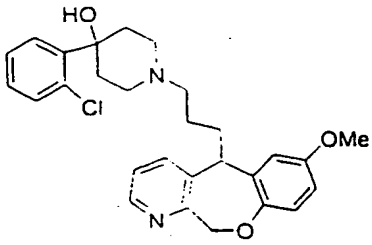


Example 91

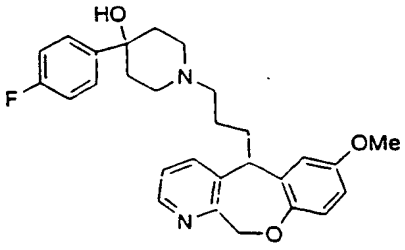
Figure 6J



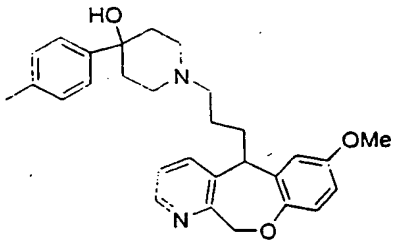
Example 92



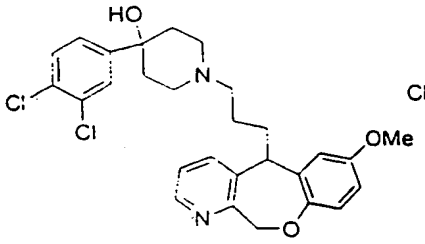
Example 93



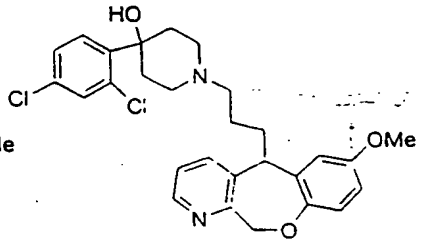
Example 94



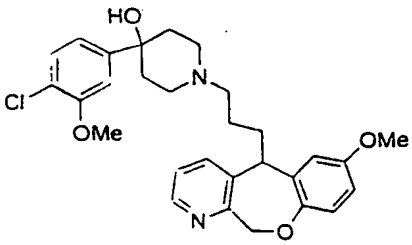
Example 95



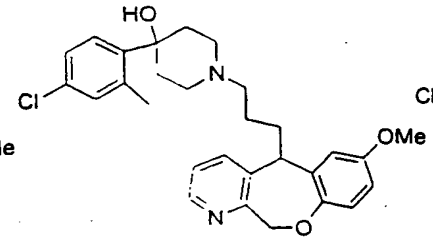
Example 96



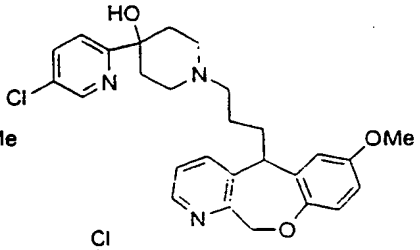
Example 97



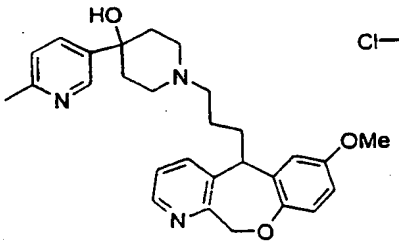
Example 98



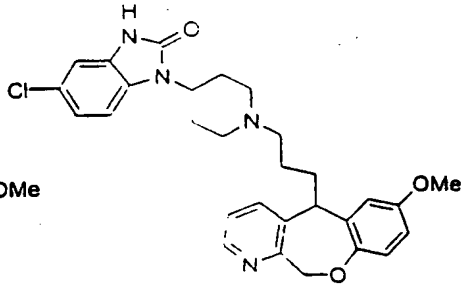
Example 99



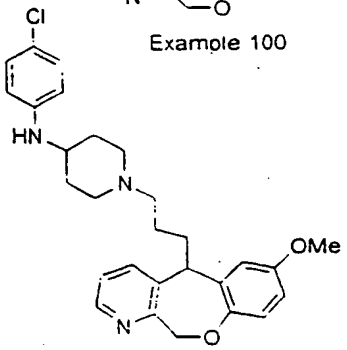
Example 100



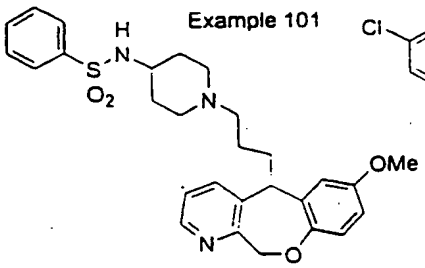
Example 101



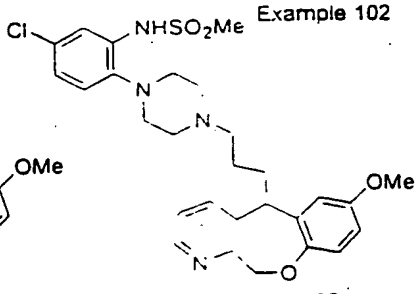
Example 102



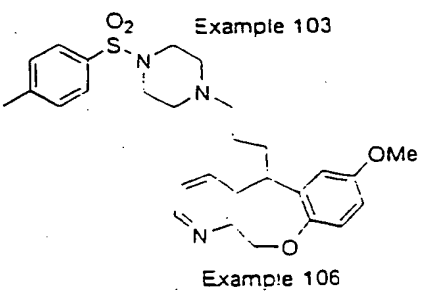
Example 103



Example 104

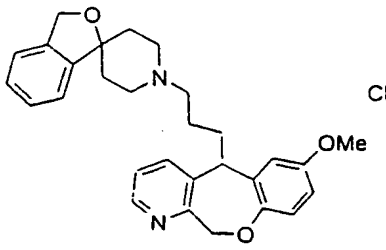


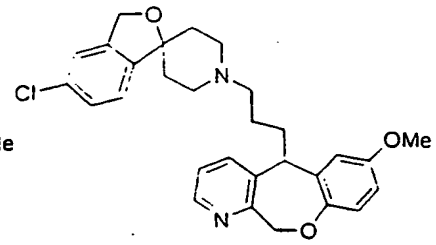
Example 105

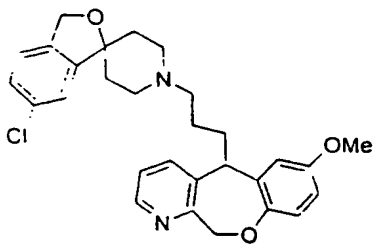


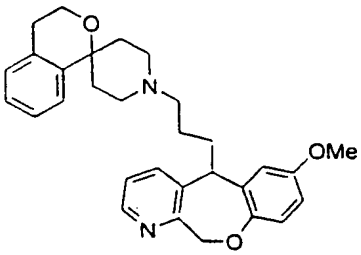
Example 106

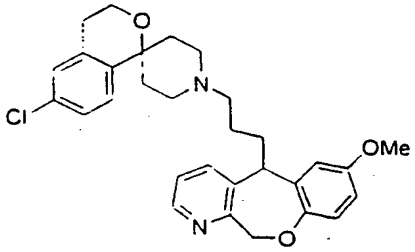
Figure 6K

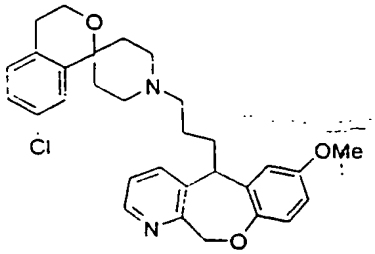

Example 107

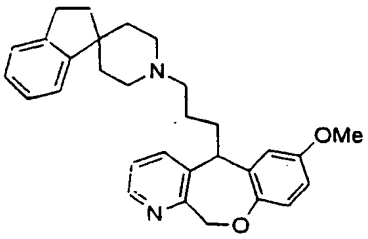

Example 108

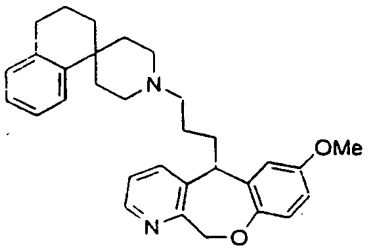

Example 109

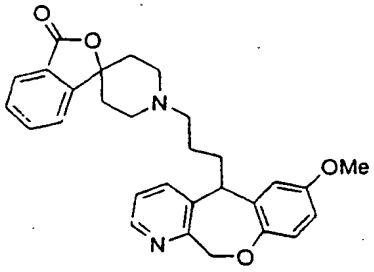

Example 110

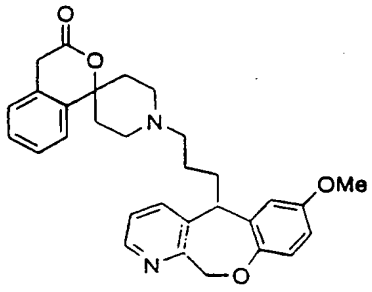

Example 111

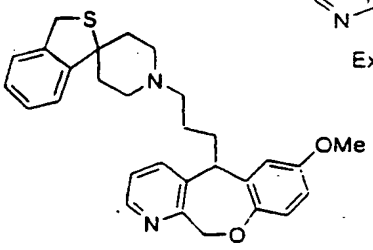

Example 112

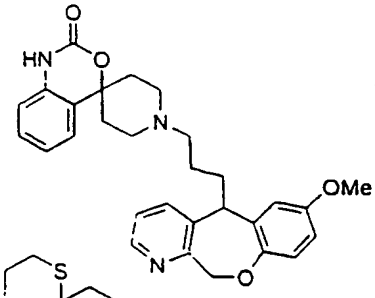

Example 113


Example 114


Example 115


Example 116


Example 118


Example 117

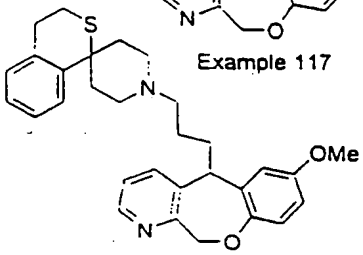
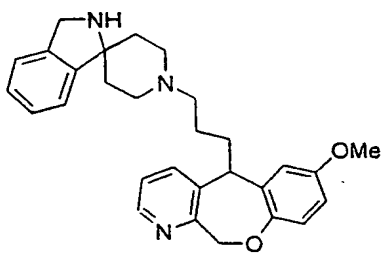
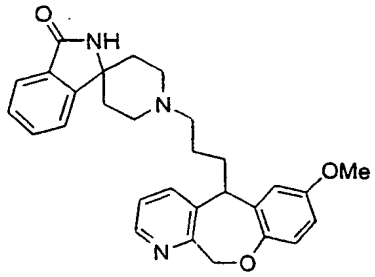

Example 119

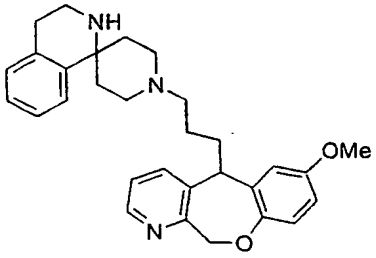
Figure 6L



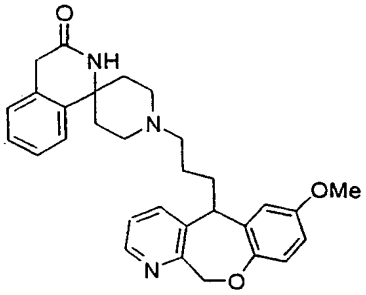
Example 120



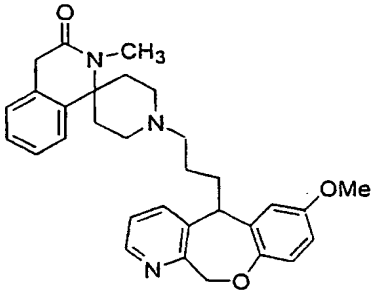
Example 121



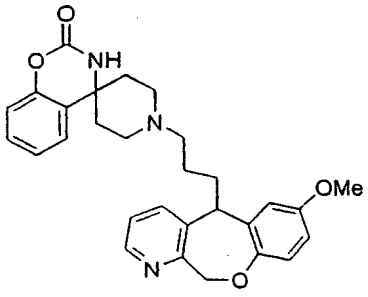
Example 122



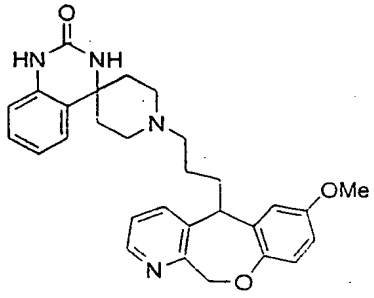
Example 123



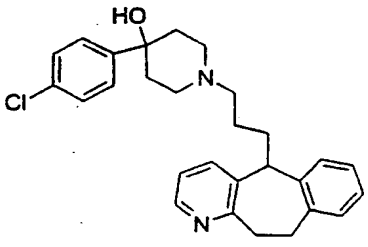
Example 124



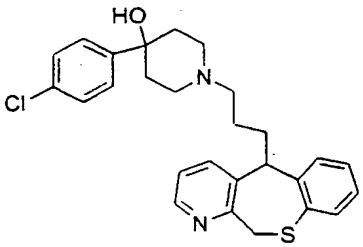
Example 125



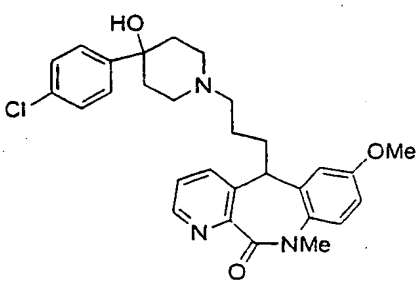
Example 126



Example 127

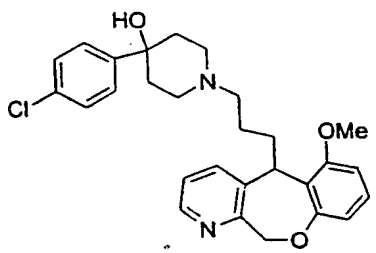


Example 128

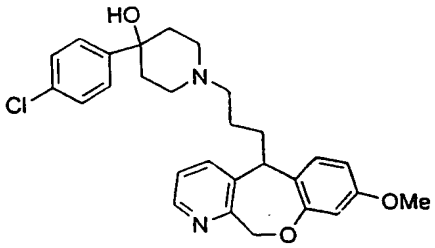


Example 129

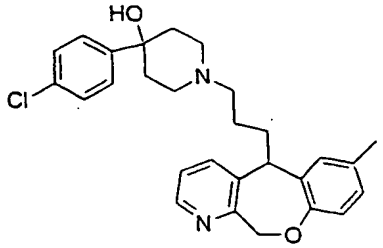
Figure 6M



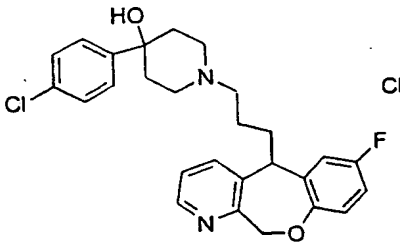
Example 130



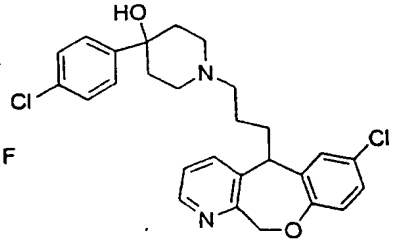
Example 131



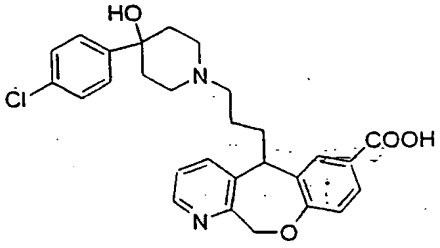
Example 132



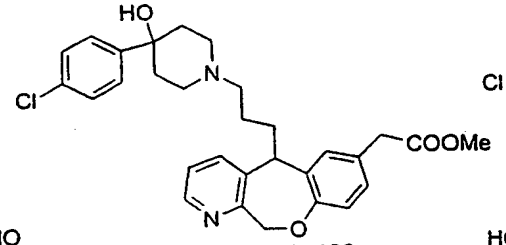
Example 133



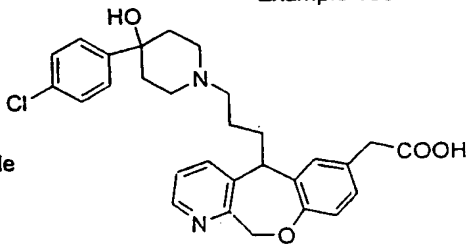
Example 134



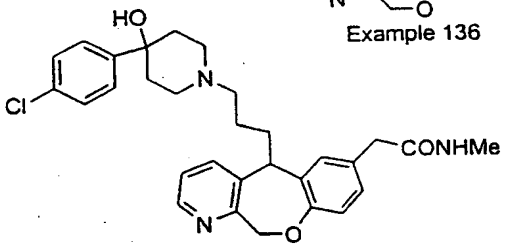
Example 135



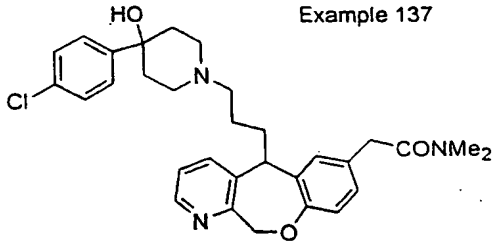
Example 136



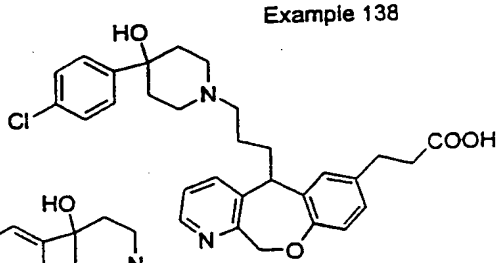
Example 137



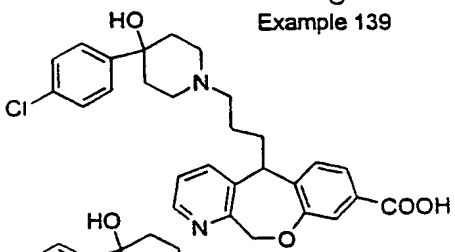
Example 138



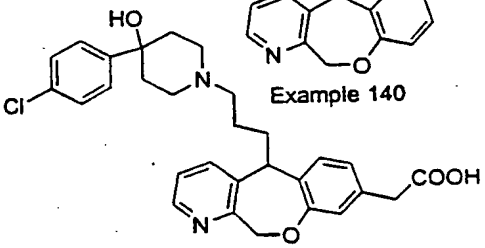
Example 139



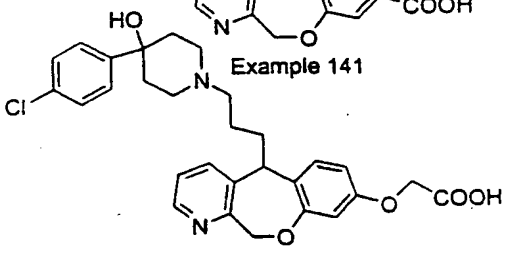
Example 140



Example 141

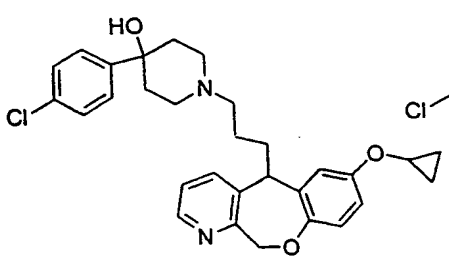


Example 142

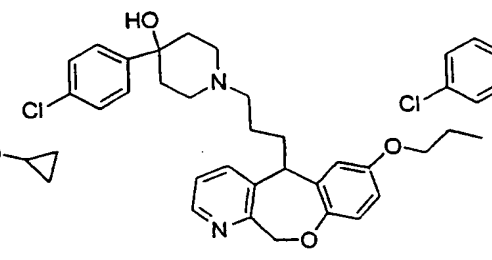


Example 143

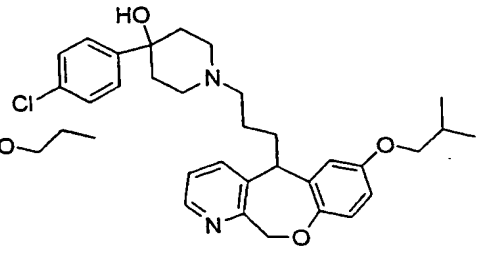
Figure 6N



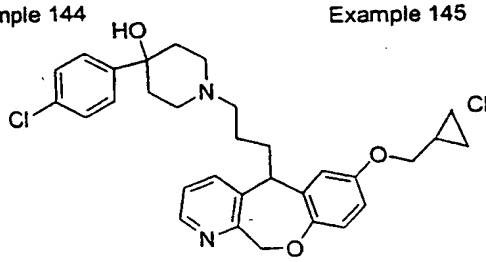
Example 144



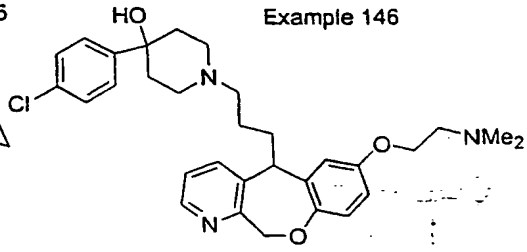
Example 145



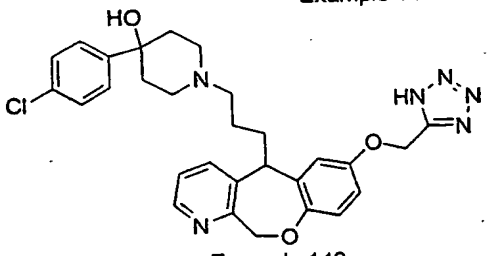
Example 146



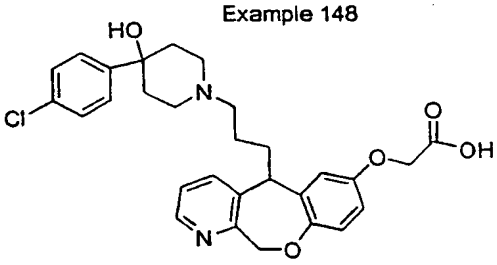
Example 147



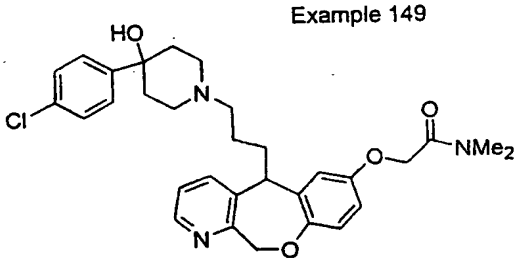
Example 148



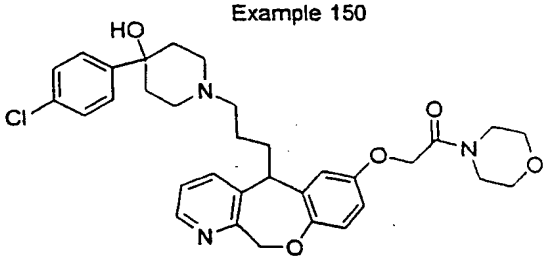
Example 149



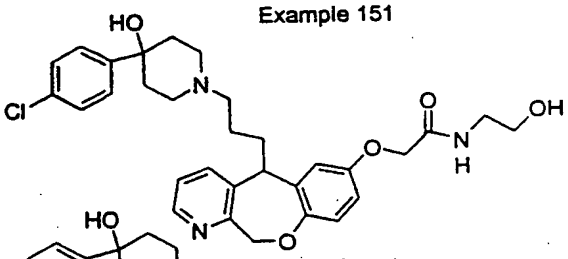
Example 150



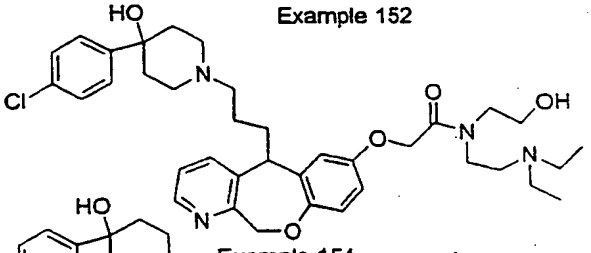
Example 151



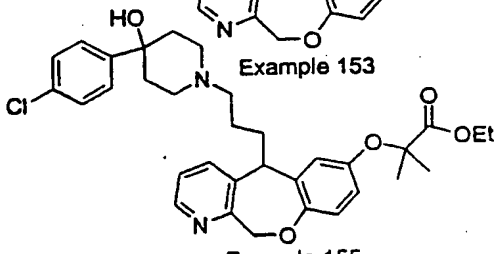
Example 152



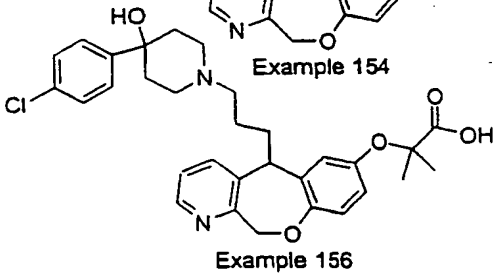
Example 153



Example 154

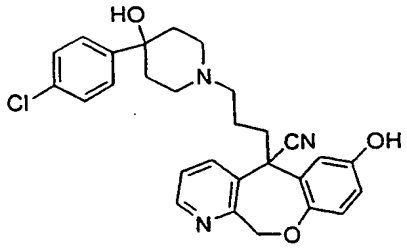


Example 155

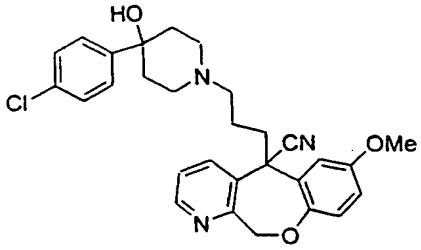


Example 156

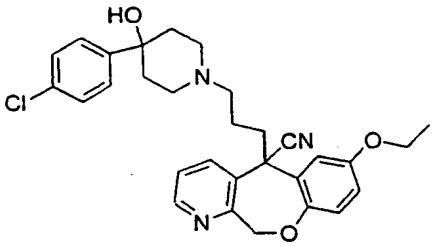
Figure 60



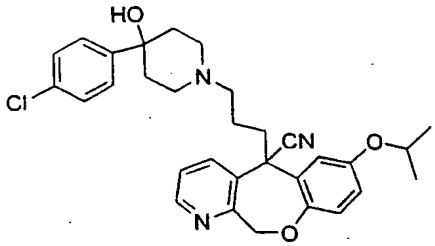
Example 157



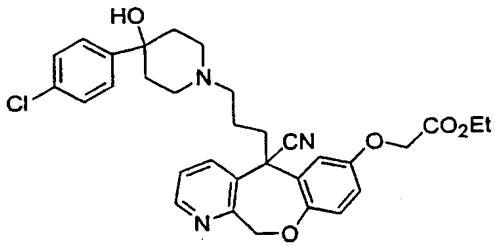
Example 158



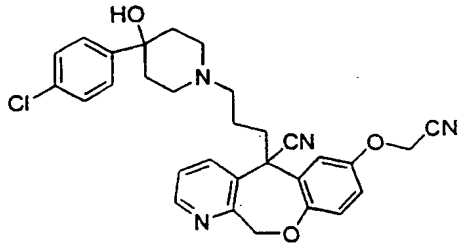
Example 159



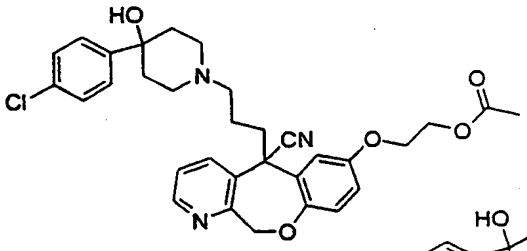
Example 160



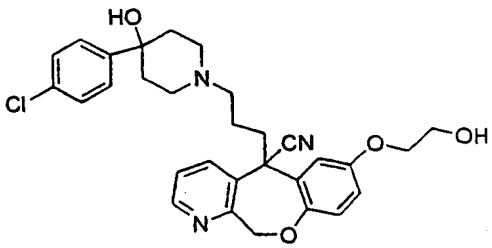
Example 161



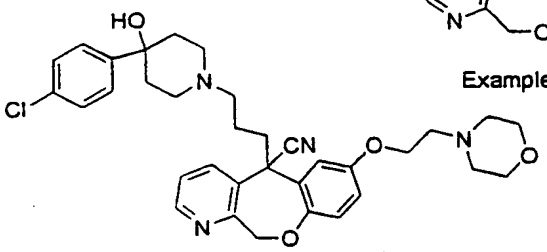
Example 162



Example 163

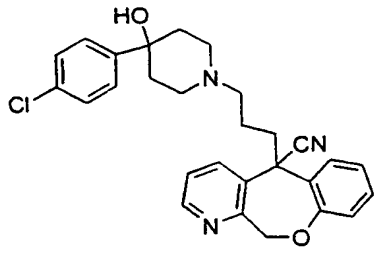


Example 164

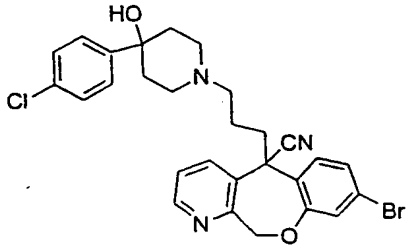


Example 165

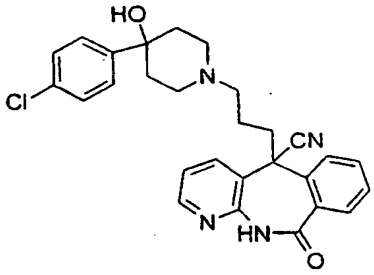
Figure 6P



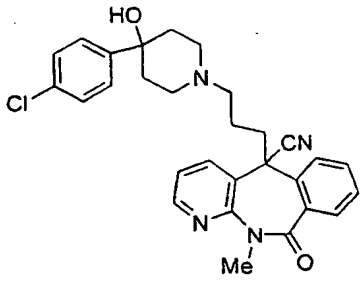
Example 166



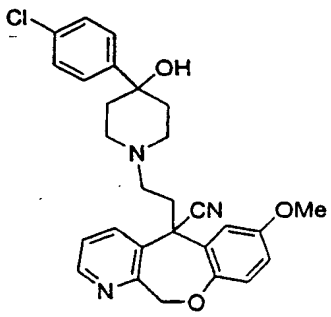
Example 167



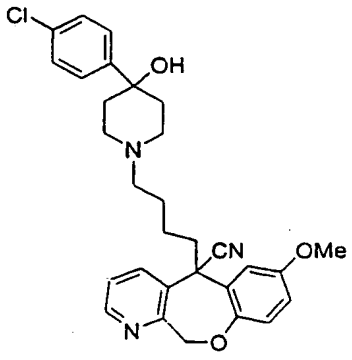
Example 168



Example 169

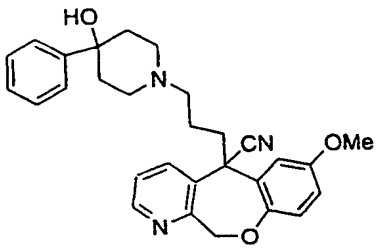


Example 170

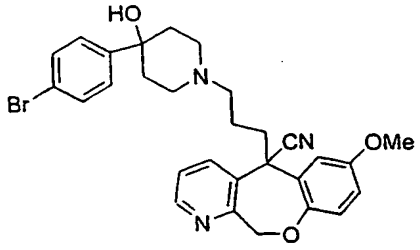


Example 171

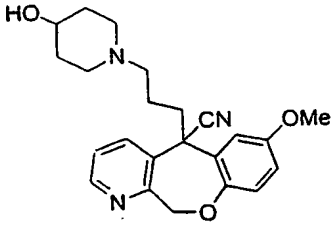
Figure 6Q



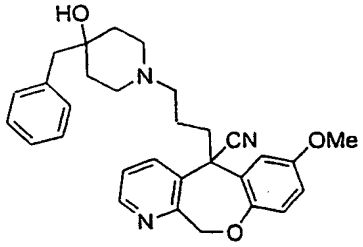
Example 172



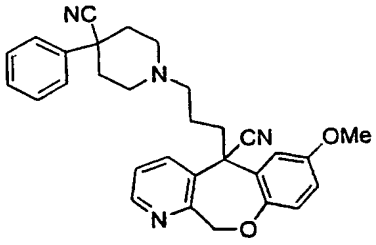
Example 173



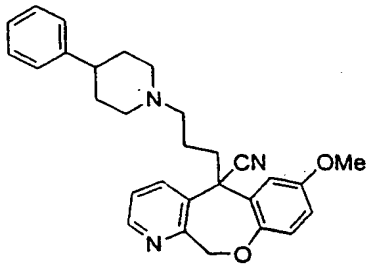
Example 174



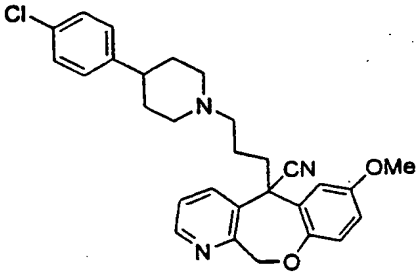
Example 175



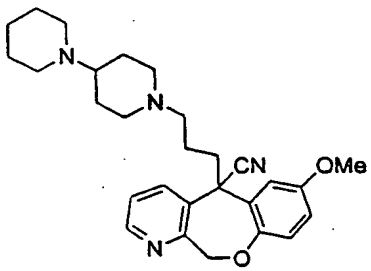
Example 176



Example 177

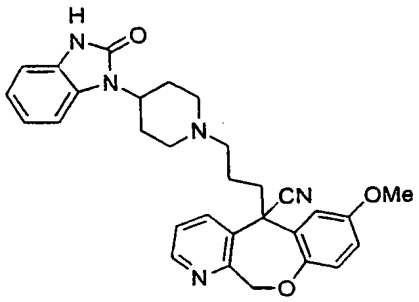


Example 178

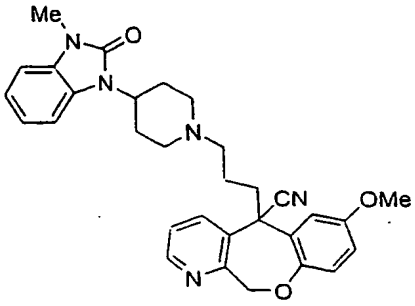


Example 179

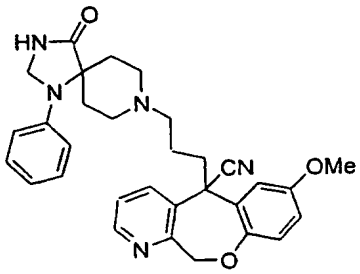
Figure 6R



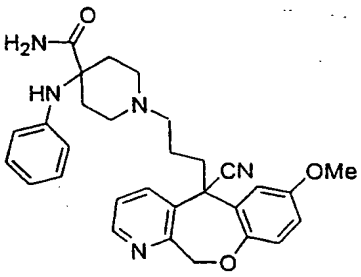
Example 180



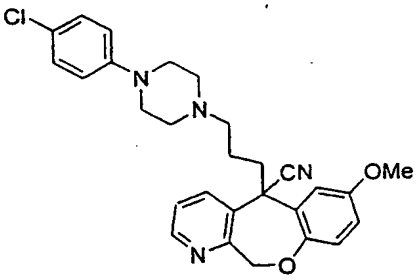
Example 181



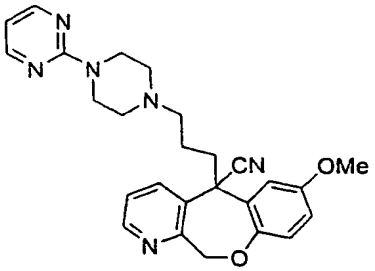
Example 182



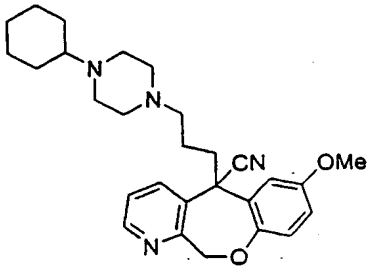
Example 183



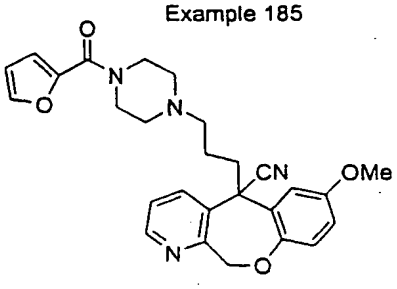
Example 184



Example 185

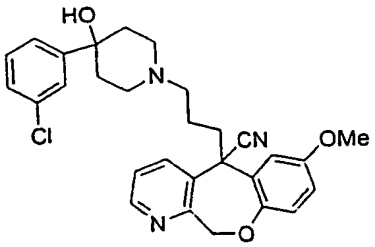


Example 186

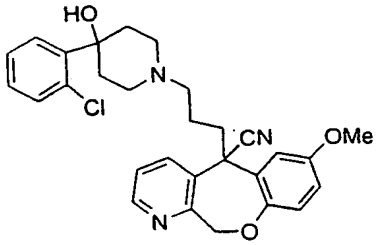


Example 187

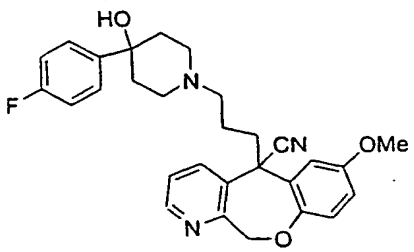
Figure 6S



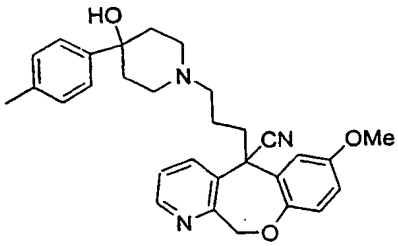
Example 188



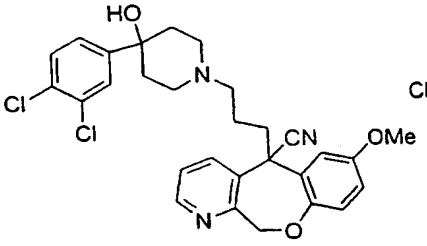
Example 189



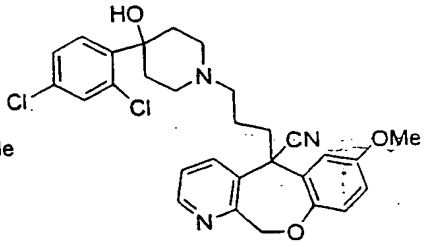
Example 190



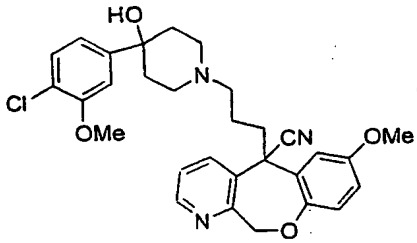
Example 191



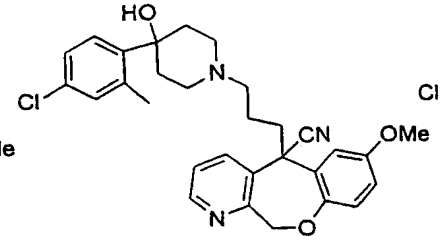
Example 192



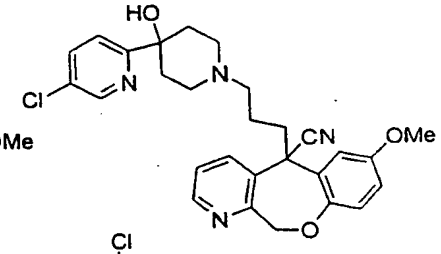
Example 193



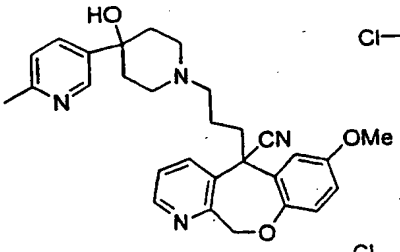
Example 194



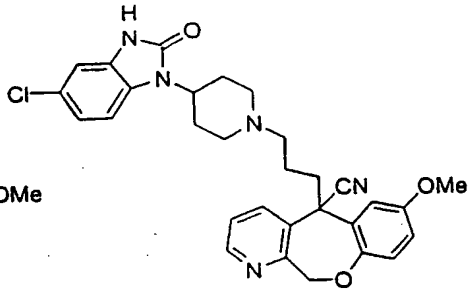
Example 195



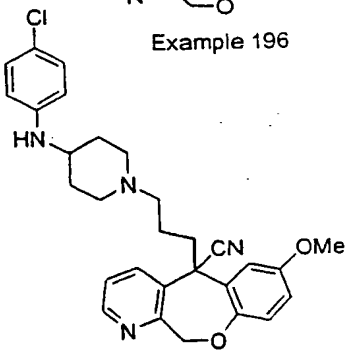
Example 196



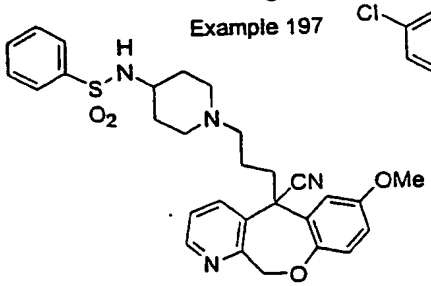
Example 197



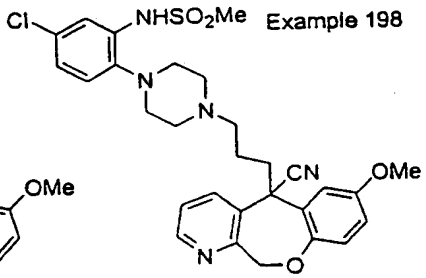
Example 198



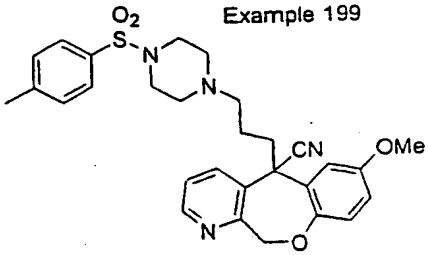
Example 199



Example 200

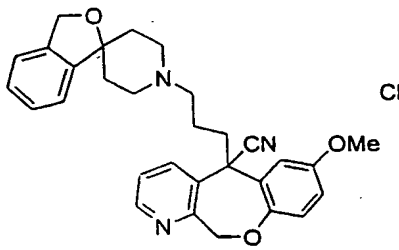


Example 201

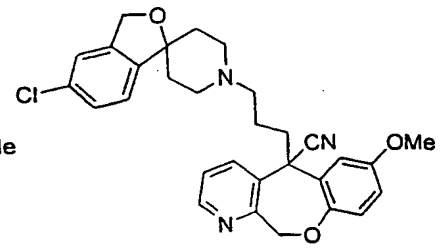


Example 202

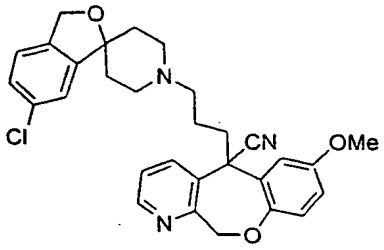
Figure 6T



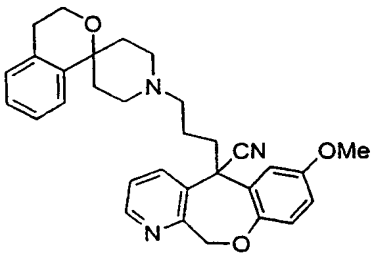
Example 203



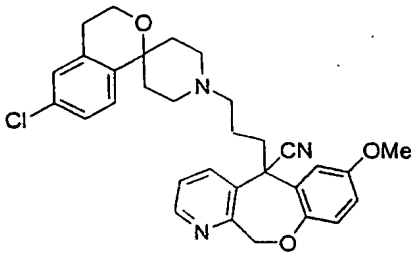
Example 204



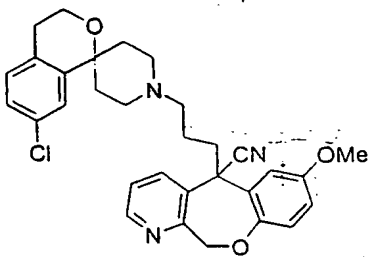
Example 205



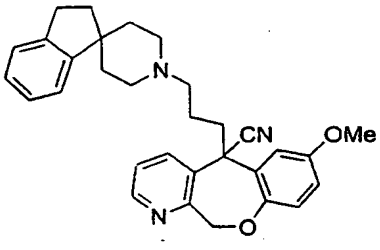
Example 206



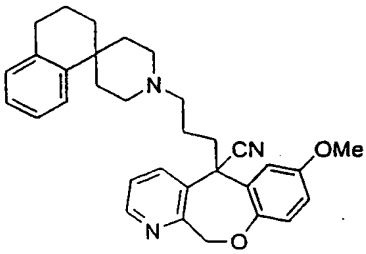
Example 207



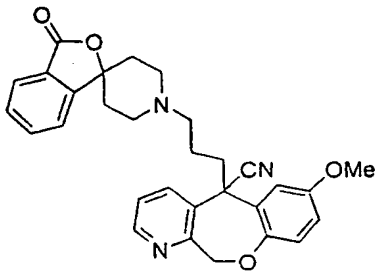
Example 208



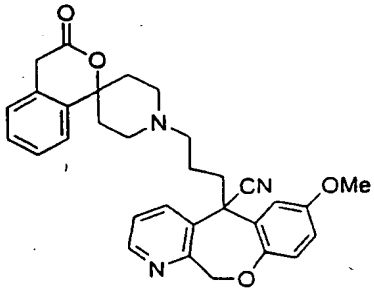
Example 209



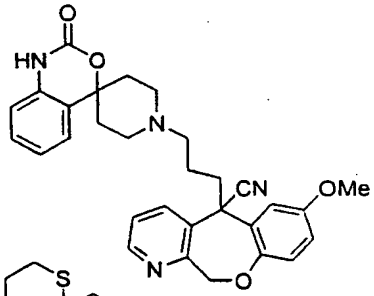
Example 210



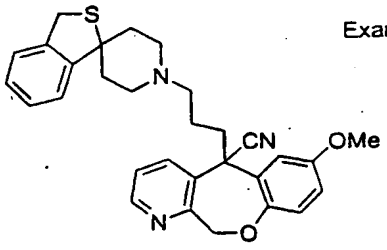
Example 211



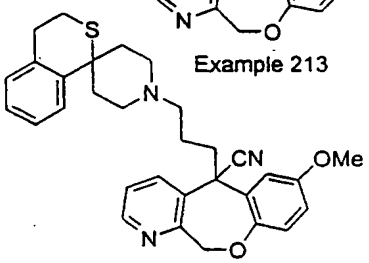
Example 212



Example 213

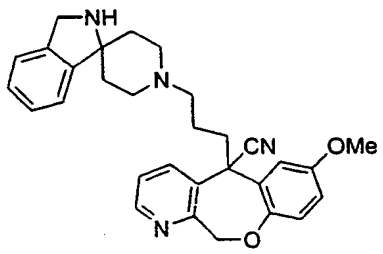


Example 214

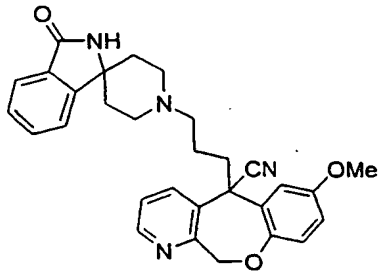


Example 215

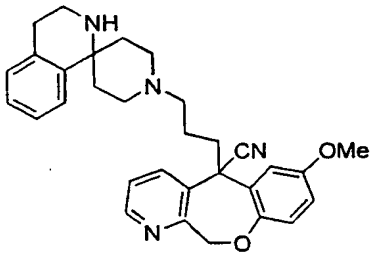
Figure 6U



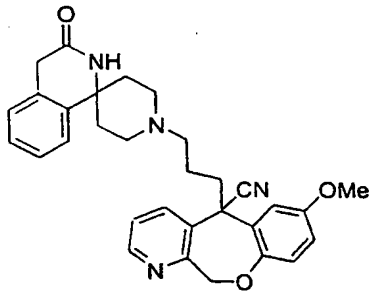
Example 216



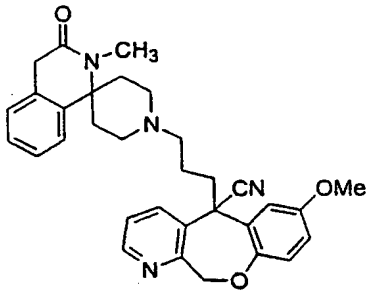
Example 217



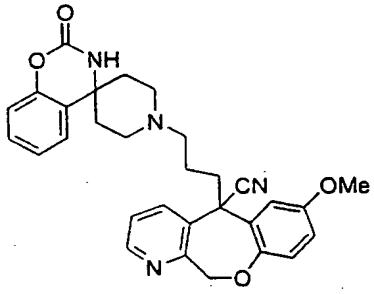
Example 218



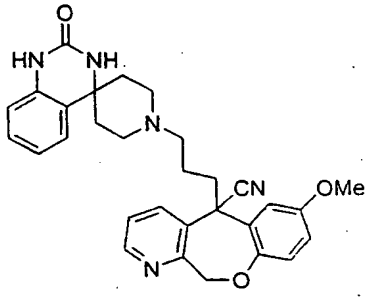
Example 219



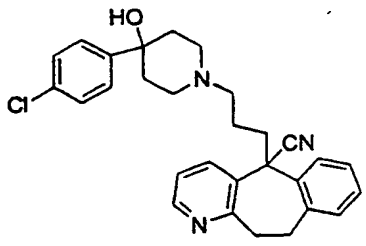
Example 220



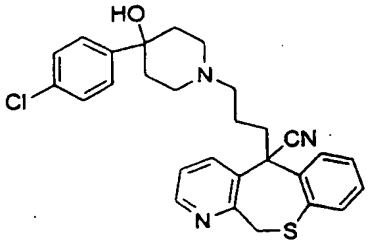
Example 221



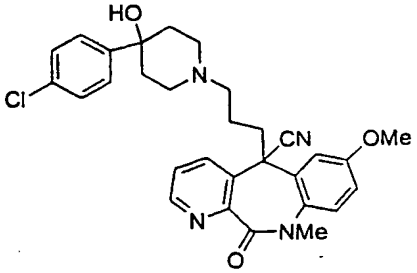
Example 222



Example 223

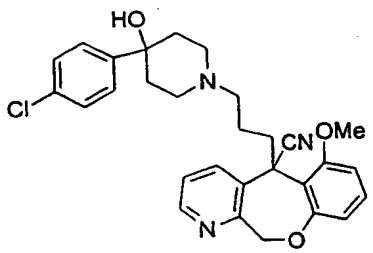


Example 224

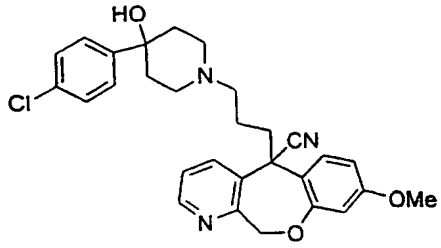


Example 225

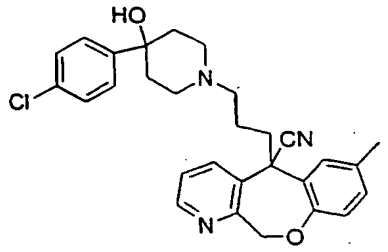
Figure 6V



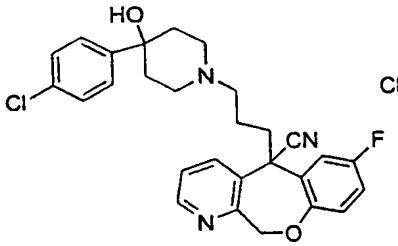
Example 226



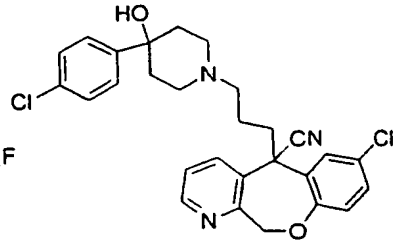
Example 227



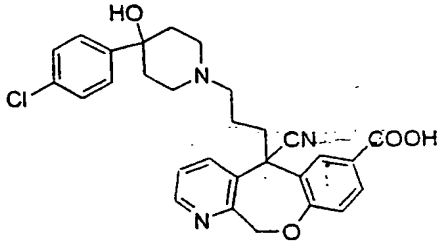
Example 228



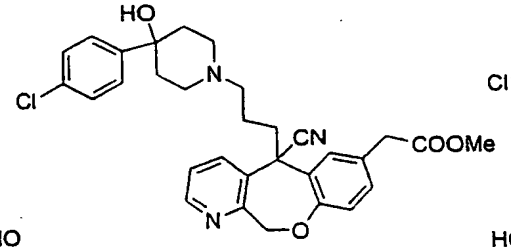
Example 229



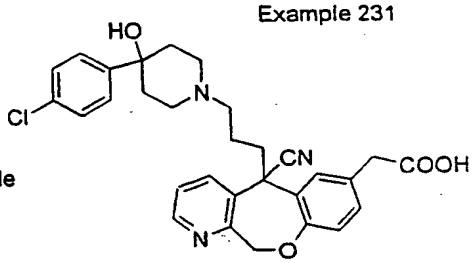
Example 230



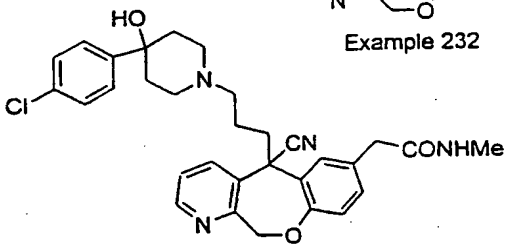
Example 231



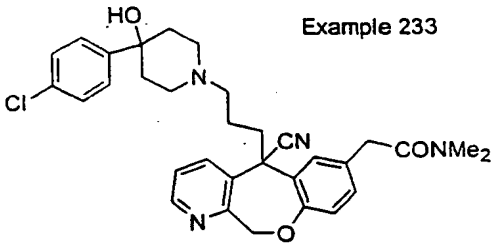
Example 232



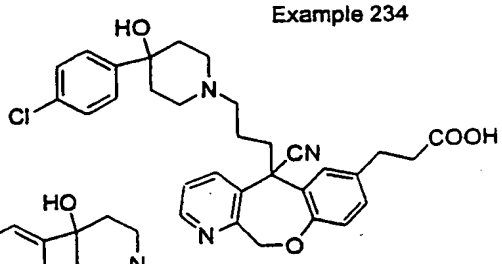
Example 233



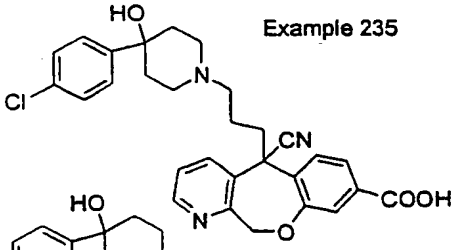
Example 234



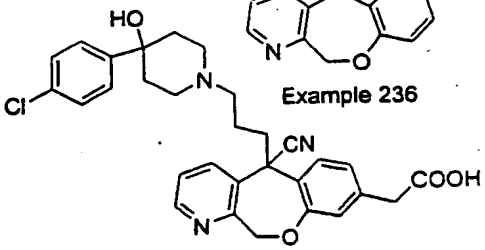
Example 235



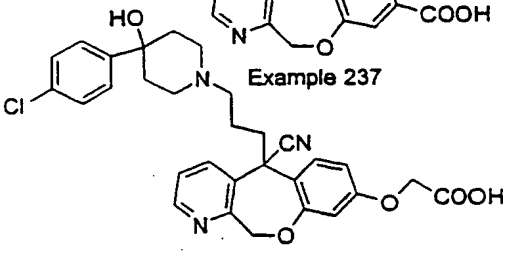
Example 236



Example 237

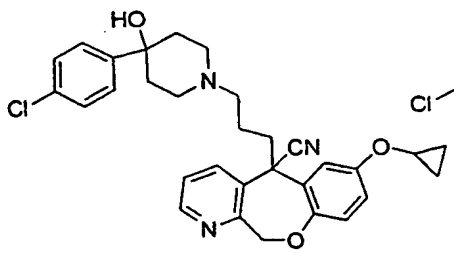


Example 238

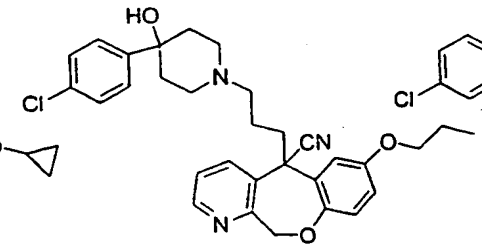


Example 239

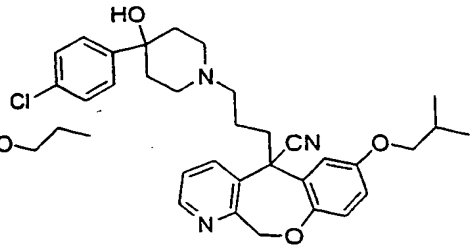
Figure 6W



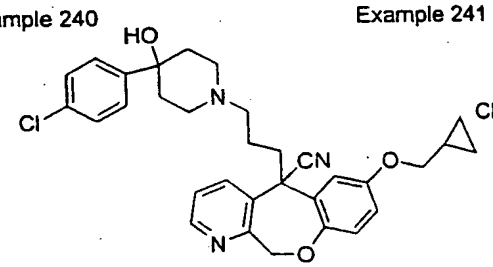
Example 240



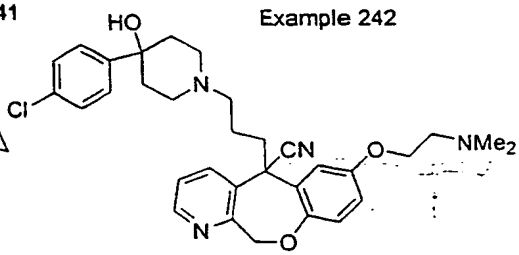
Example 241



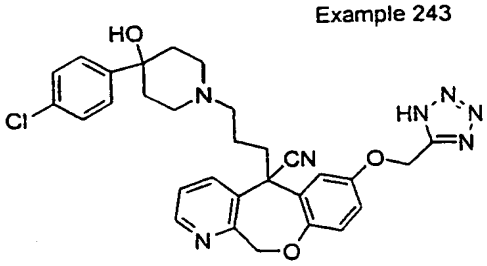
Example 242



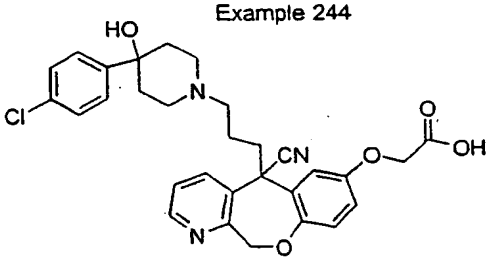
Example 243



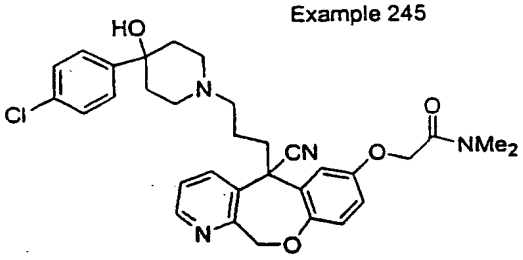
Example 244



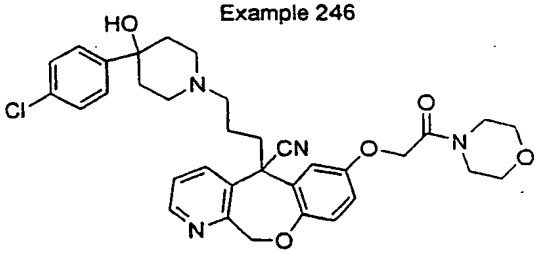
Example 245



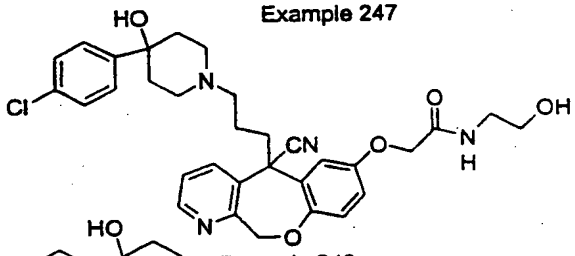
Example 246



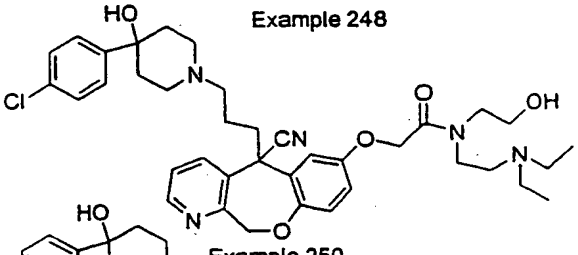
Example 247



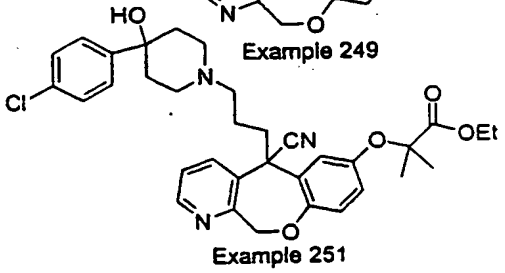
Example 248



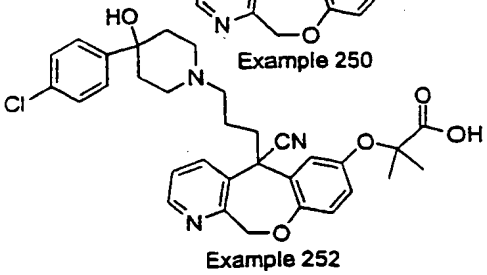
Example 249



Example 250

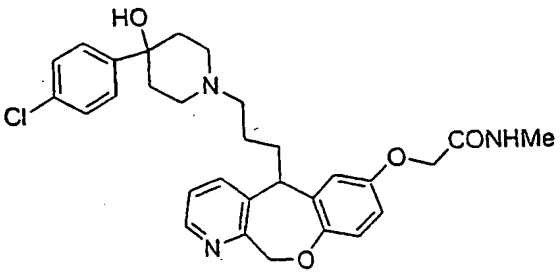


Example 251

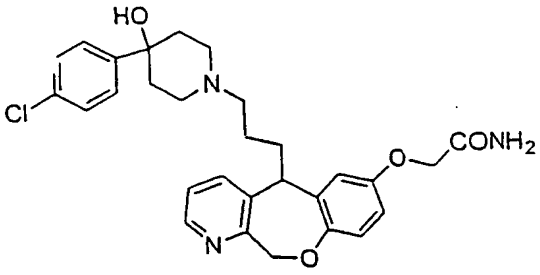


Example 252

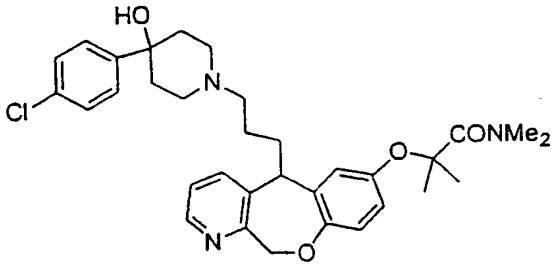
Figure 6X



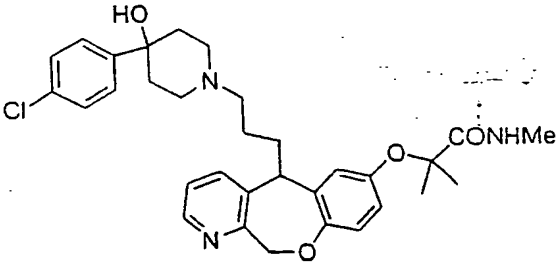
Example 253



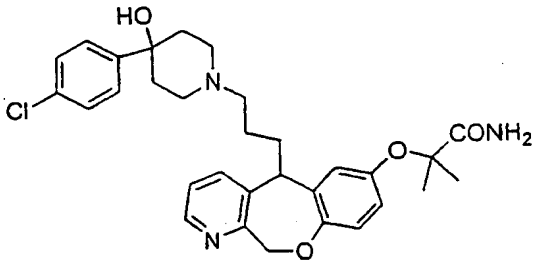
Example 254



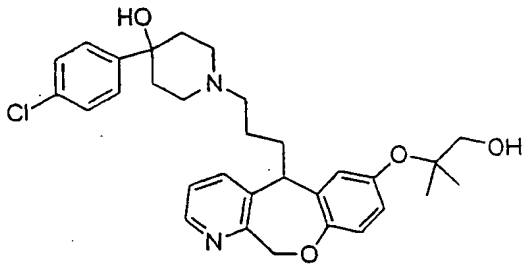
Example 255



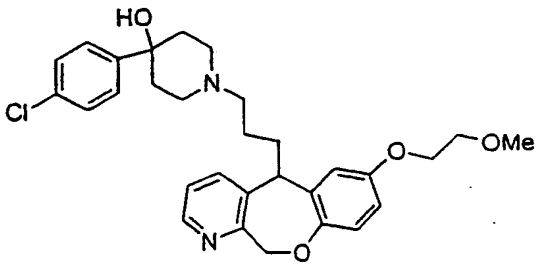
Example 256



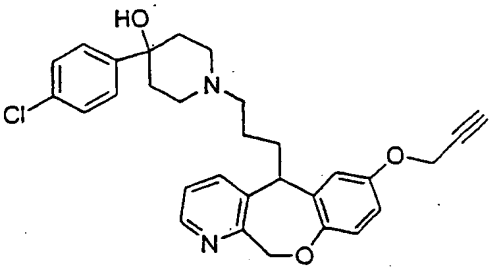
Example 257



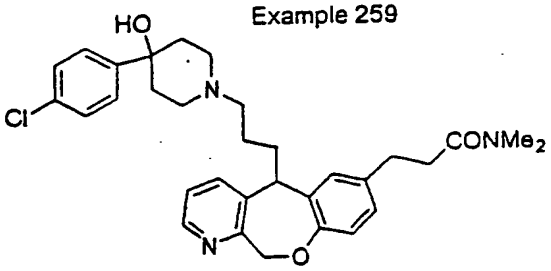
Example 258



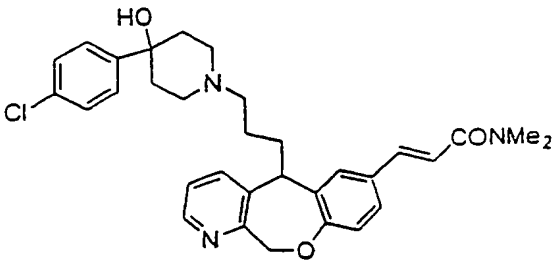
Example 259



Example 260

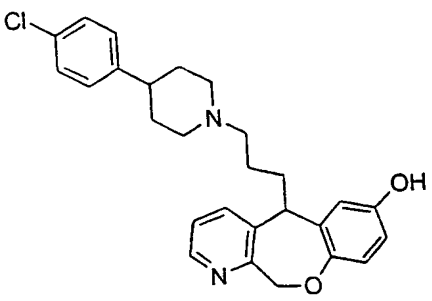


Example 261

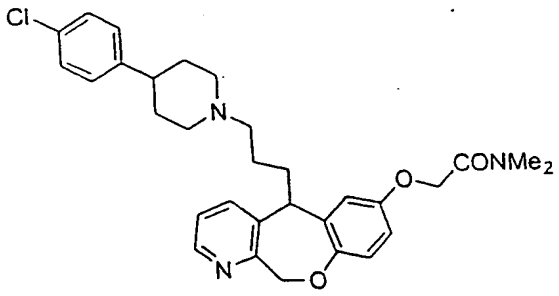


Example 262

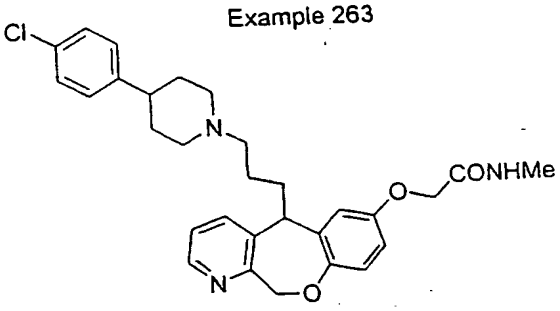
Figure 6Y



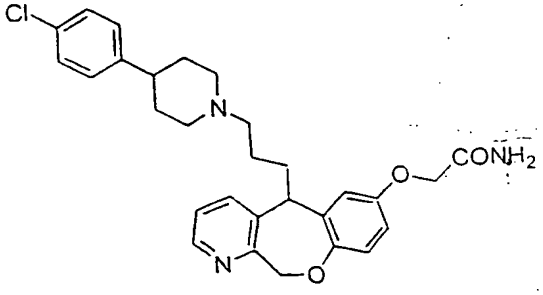
Example 263



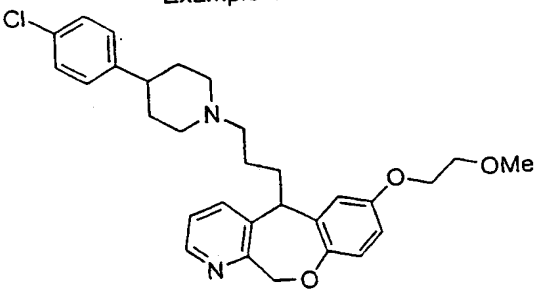
Example 264



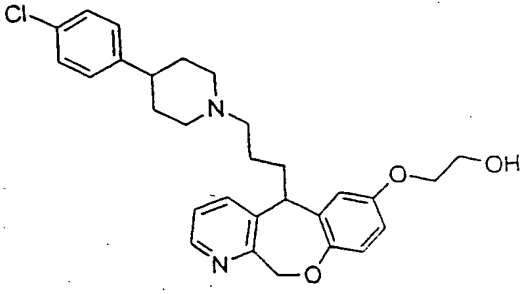
Example 265



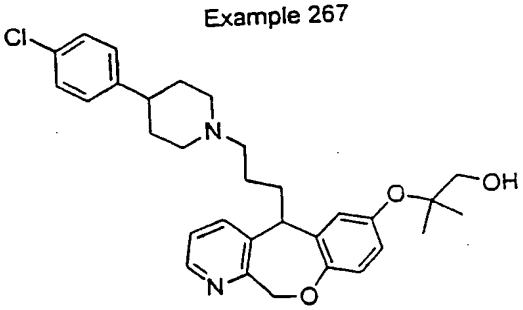
Example 266



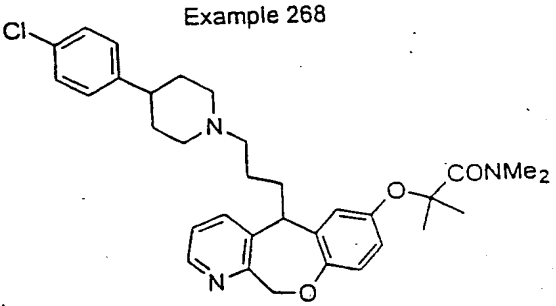
Example 267



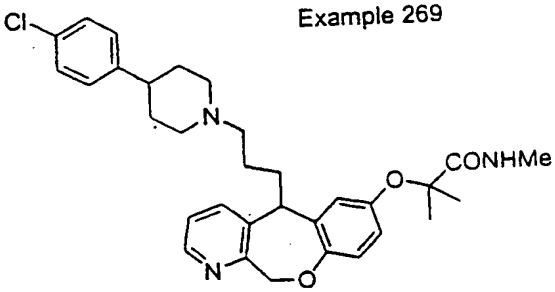
Example 268



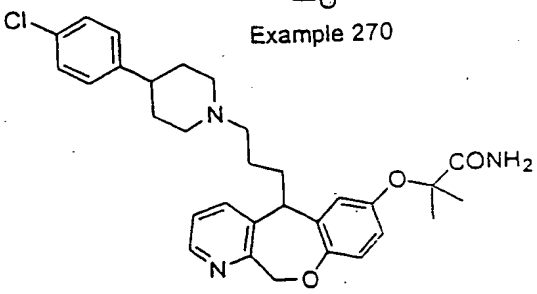
Example 269



Example 270

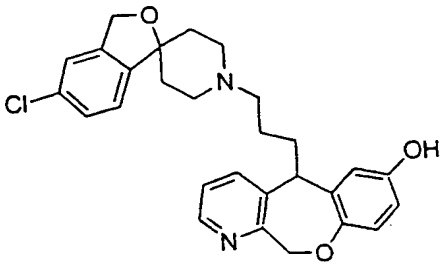


Example 271

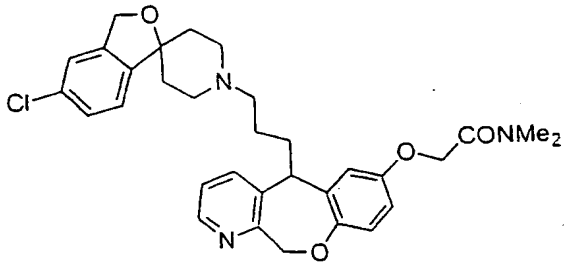


Example 272

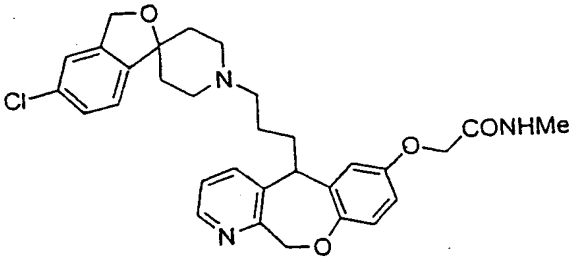
Figure 6Z



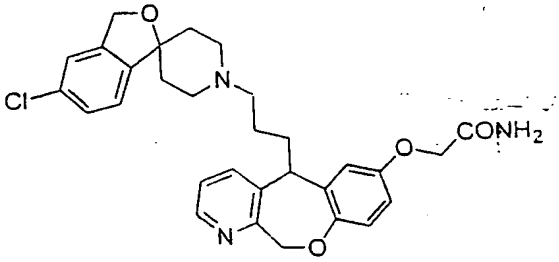
Example 273



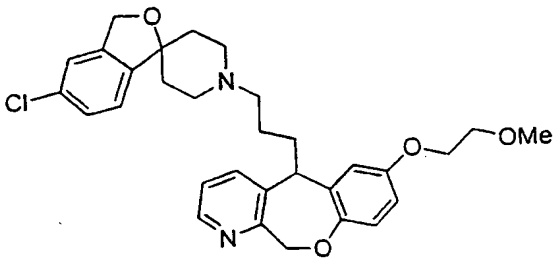
Example 274



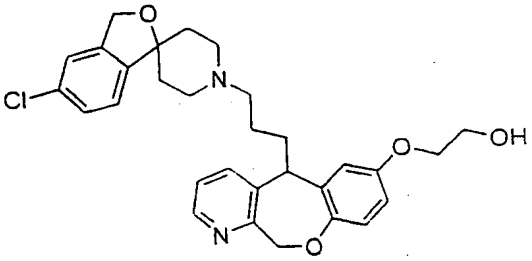
Example 275



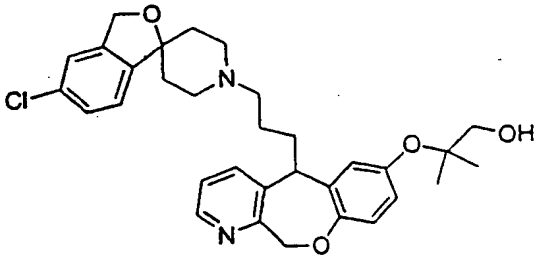
Example 276



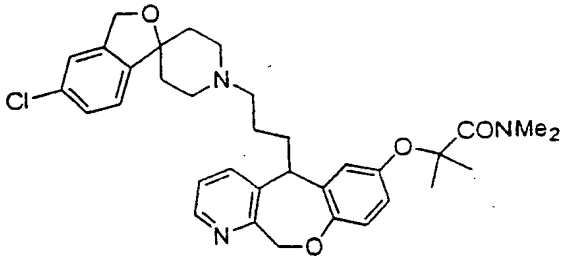
Example 277



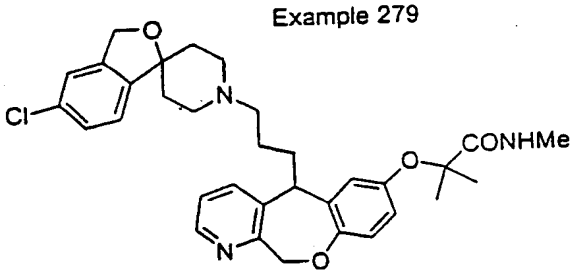
Example 278



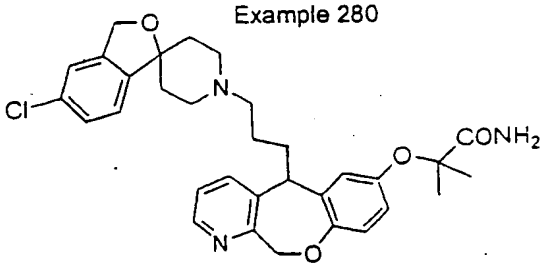
Example 279



Example 280

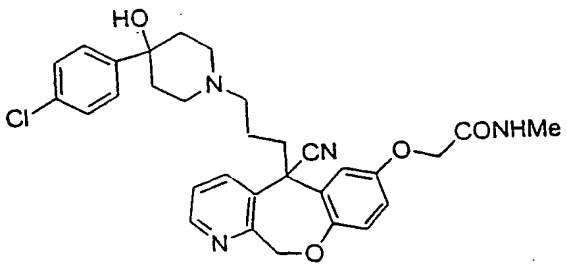


Example 281

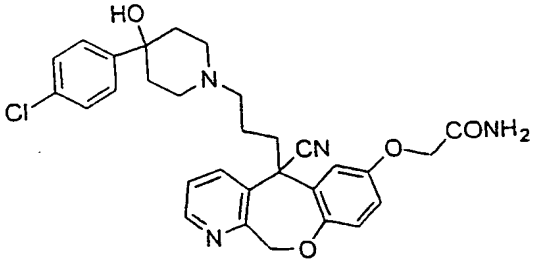


Example 282

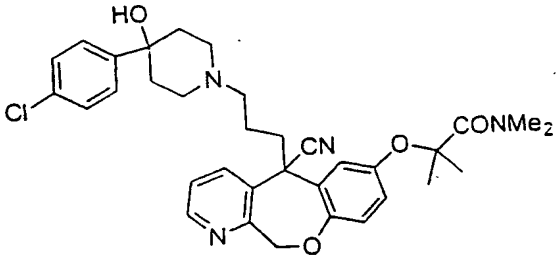
Figure 6AA



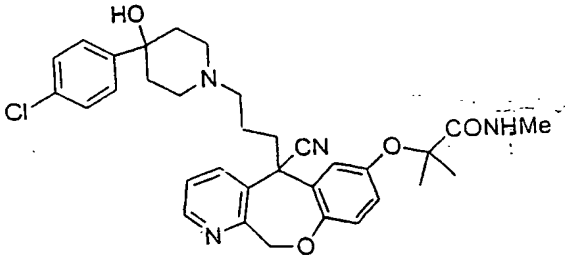
Example 283



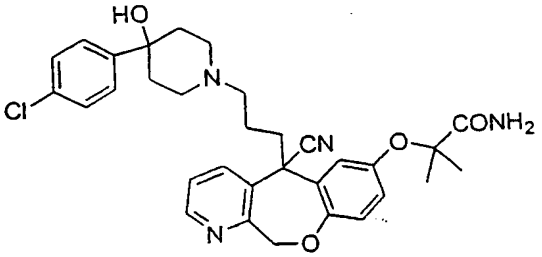
Example 284



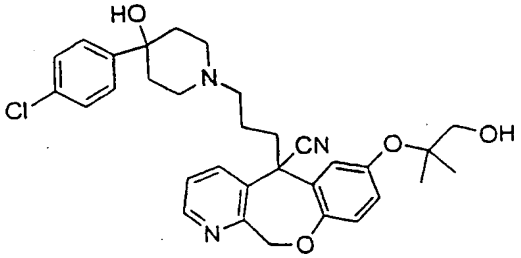
Example 285



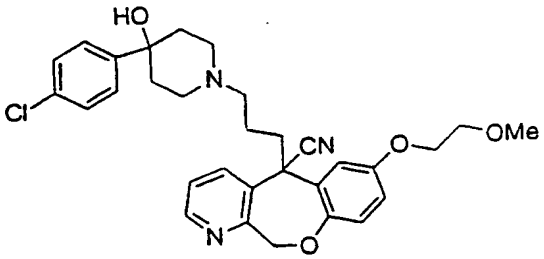
Example 286



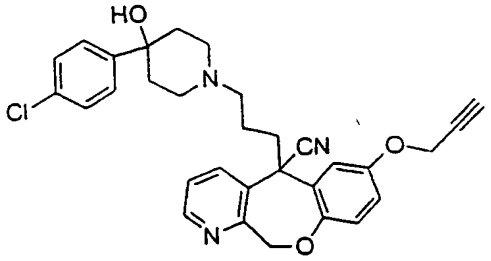
Example 287



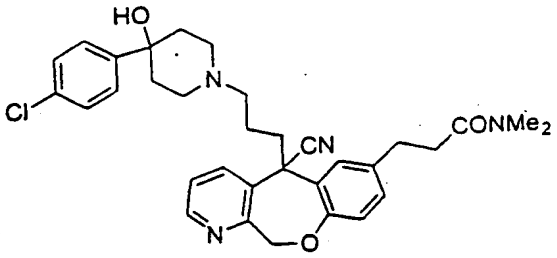
Example 288



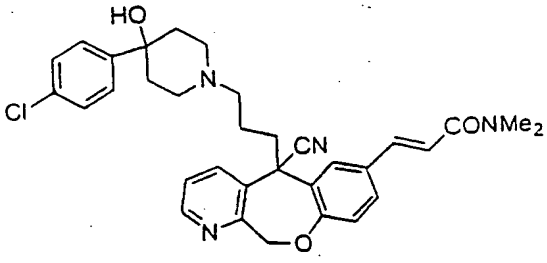
Example 289



Example 290

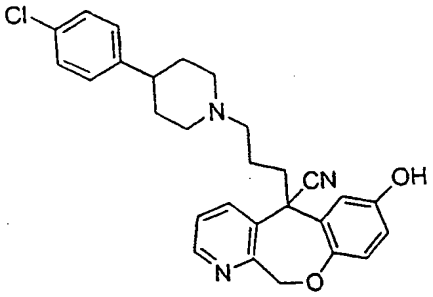


Example 291

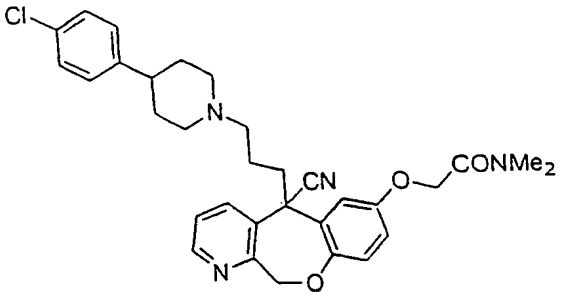


Example 292

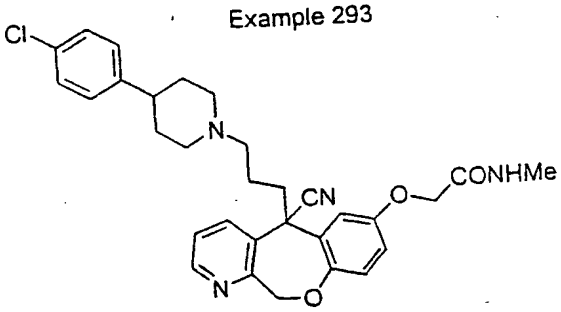
Figure 6AB



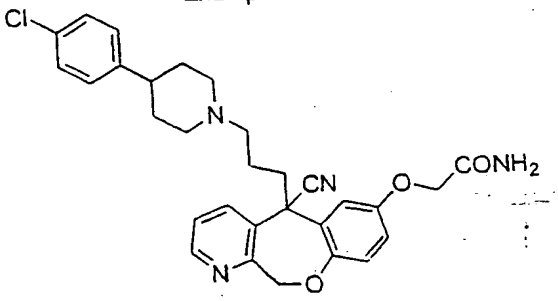
Example 293



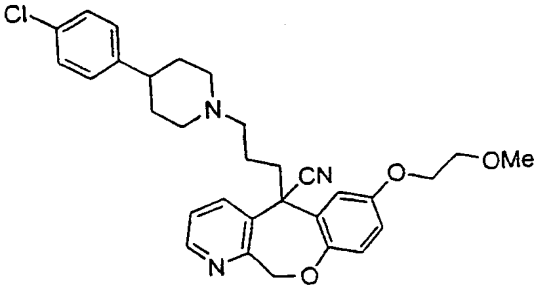
Example 294



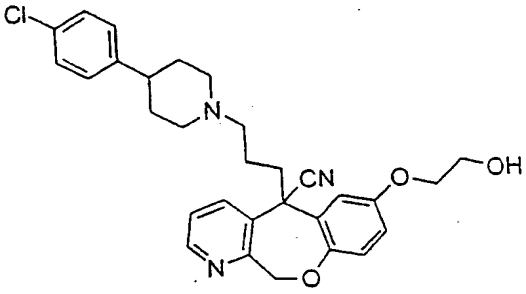
Example 295



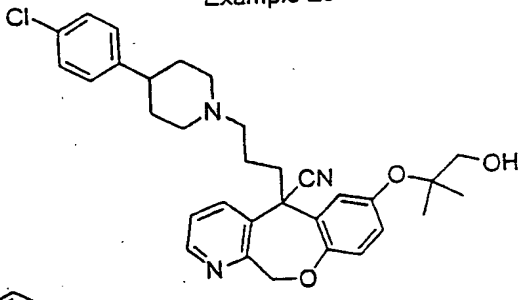
Example 296



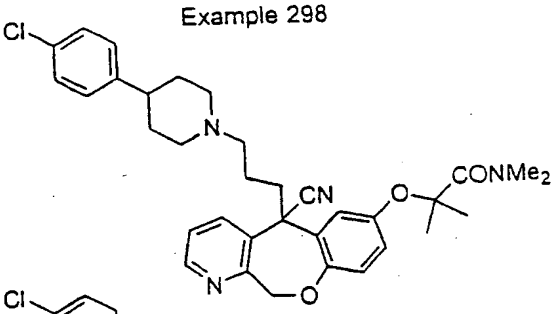
Example 297



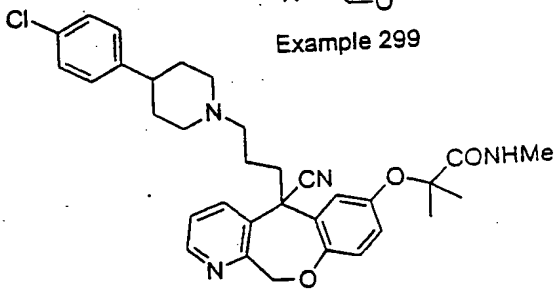
Example 298



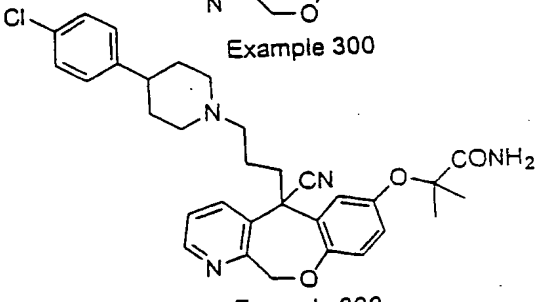
Example 299



Example 300

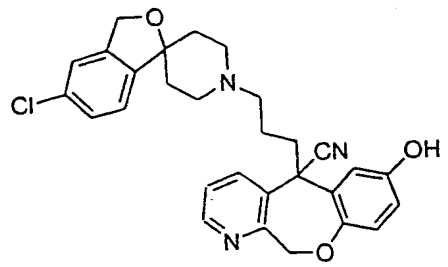


Example 301

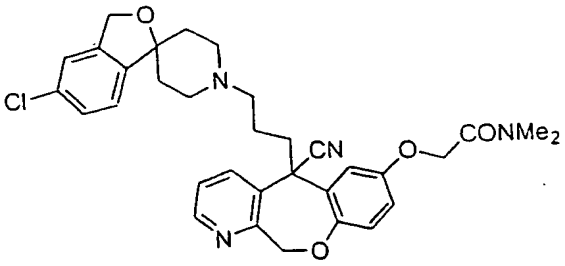


Example 302

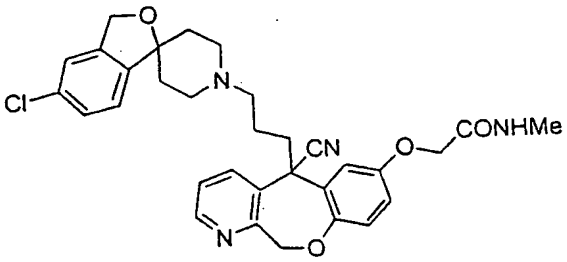
Figure 6AC



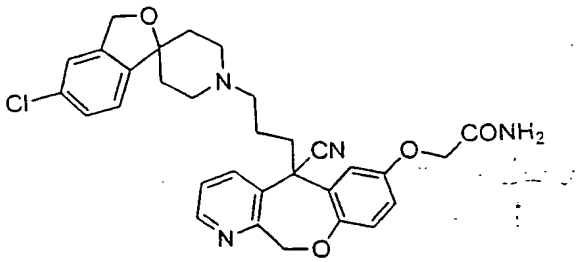
Example 303



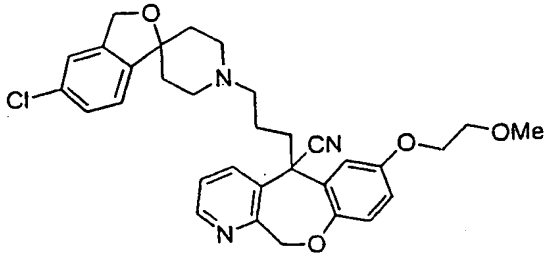
Example 304



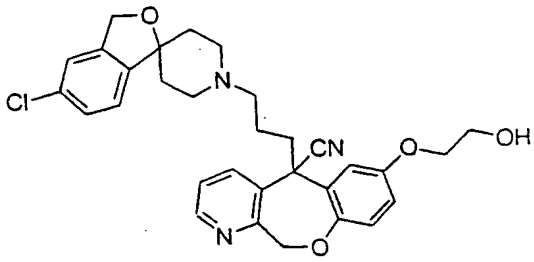
Example 305



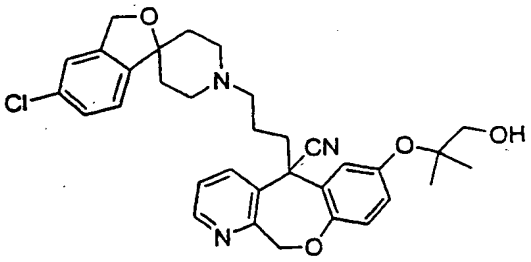
Example 306



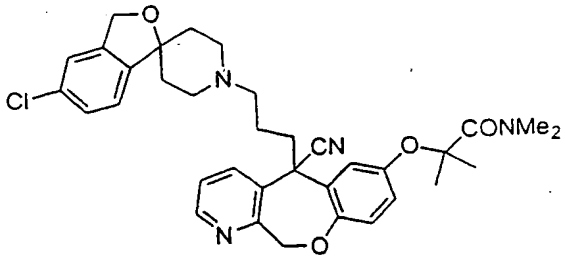
Example 307



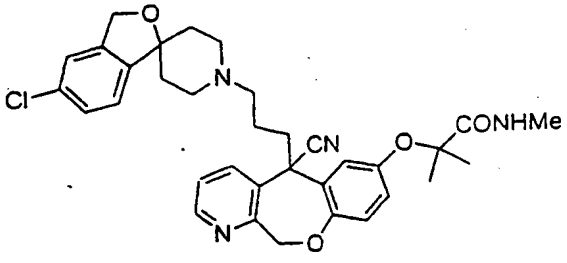
Example 308



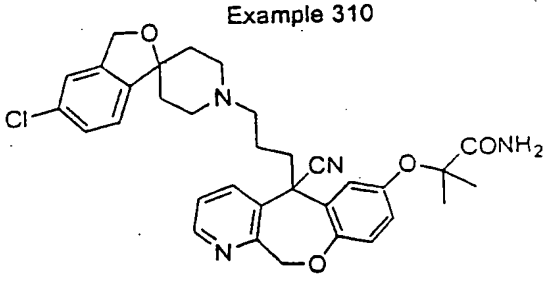
Example 309



Example 310



Example 311



Example 312

Figure 6AD

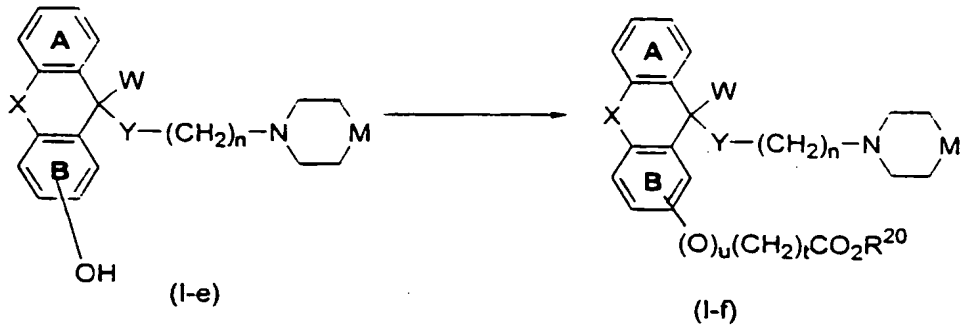


Figure 7

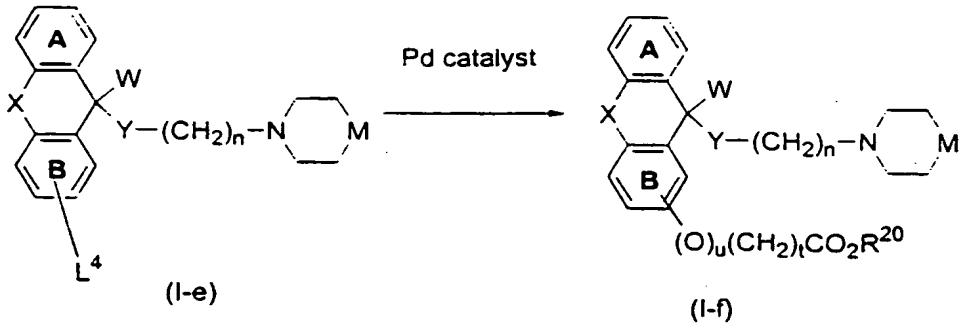

A
W
X
Y—(CH2)n—N
M
B
L4
(I-e)
Pd catalyst
A
W
X
Y—(CH2)n—N
M
B
(O)u(CH2)tCO2R20
(I-f)

Figure 8

INTERNATIONAL SEARCH REPORT

Interna .al Application No
PCT/US 99/01367

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D221/16 C07D225/08 C07D313/10 C07D491/044 C07D495/04
A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 98 02151 A (LEUCOSITE INC) 22 January 1998 ---	1-90
A	WO 96 31477 A (SCHERING CORPORATION) 10 October 1996 see the whole document & US 5 672 611 A cited in the application ---	1-90
A	EP 0 341 860 A (SCHERING CORPORATION) 15 November 1989 see claims 1-16 & WO 89 10369 A cited in the application --- -/--	1-90

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 May 1999	17/05/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Siatou, E

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/US 99/01367

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 524 784 A (SCHERING CORPORATION) 27 January 1993 see claims 1-15 & WO 93 02081 A cited in the application	1-90
A	EP 0 515 158 A (SCHERING CORPORATION) 25 November 1992 see claims 1-9 & WO 92 20681 A cited in the application	1-90
A	US 3 409 621 A (F. J. VILLANI ET AL) 5 November 1968 see the whole document	1-90

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/01367

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-46, 81, 90
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-46, 81, 90 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna .al Application No
PCT/US 99/01367

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9802151 A	22-01-1998	AU 3659897 A	09-02-1998
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